Large-scale association analysis identifies new risk loci for coronary artery disease

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Supplementary Figures

Supplementary Figure 1: Flow-chart of the CARDIoGRAMplusC4D study

Supplementary Figure 2: Histogram of the absolute meta-analysis z-scores for the replication SNPs in Stage 2

Supplementary Figure 3: Forest plots of the 15 novel coronary artery disease loci

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Supplementary Tables

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Supplementary Note

1. Study characteristics

2. Background information on novel coronary artery disease risk loci

3. Network analysis in genes not associated to CAD

4. Sources of Funding

5. Consortia

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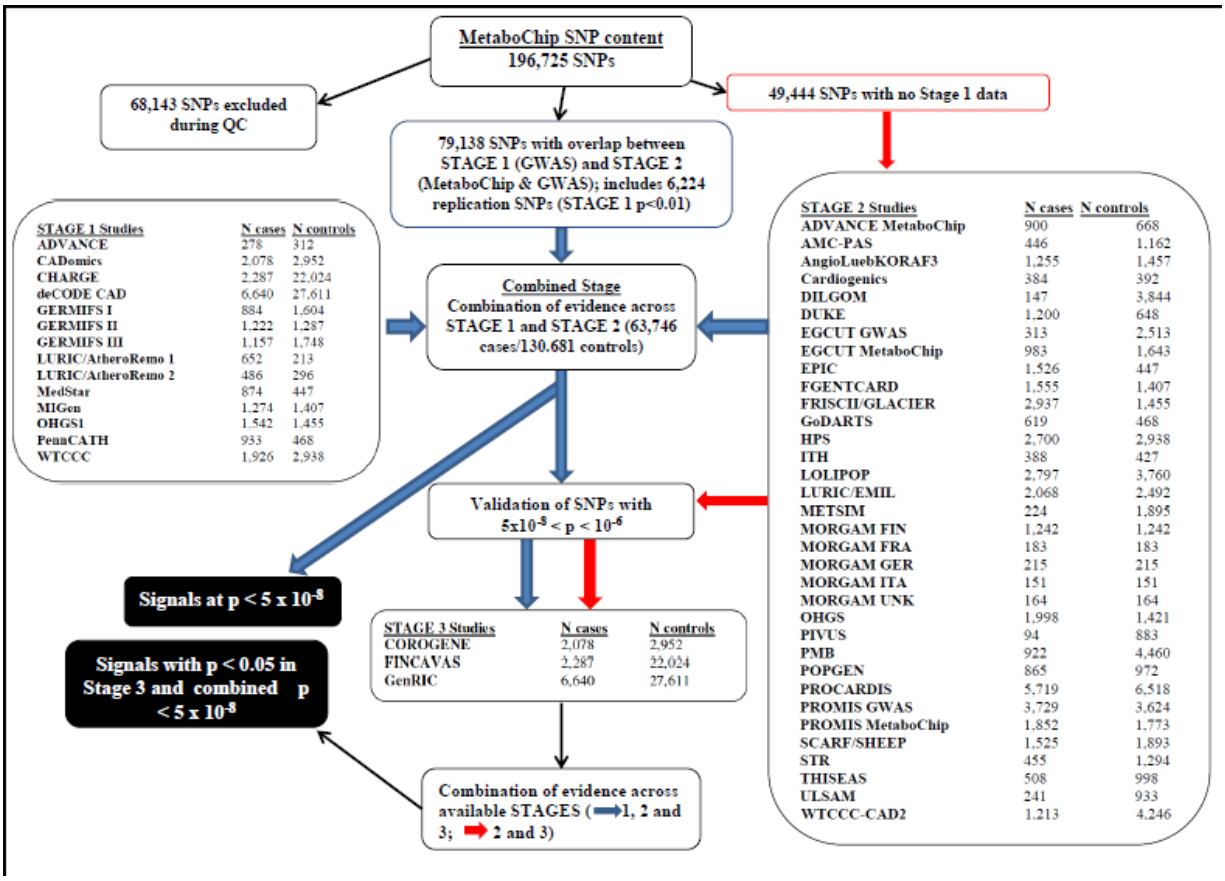
Supplementary Figures

Supplementary Figure 1: Flow-chart of the CARDIoGRAMplusC4D study. The 196,725 SNP markers on the Metabochip array were selected by a number of consortia working on cardiometabolic traits with the aim to perform extensive replication of initial signals from large GWA meta-analyses and undertake fine-mapping in already known loci. Circa 30% of the markers on this array were not polymorphic in Caucasian studies mainly due to the use of an early release of the 1000 Genomes (July 2009) for selecting SNPs for fine-mapping analysis. Blue arrows mark the path of analysing the 79,138 SNPs with data in both Stage 1 and 2 studies (includes all replication SNPs submitted by CARDIoGRAM) whereas red arrows mark the path of analysing the remaining 49,444 polymorphic SNPs with data only in stage 2 studies (mainly those profiled with the Metabochip array).



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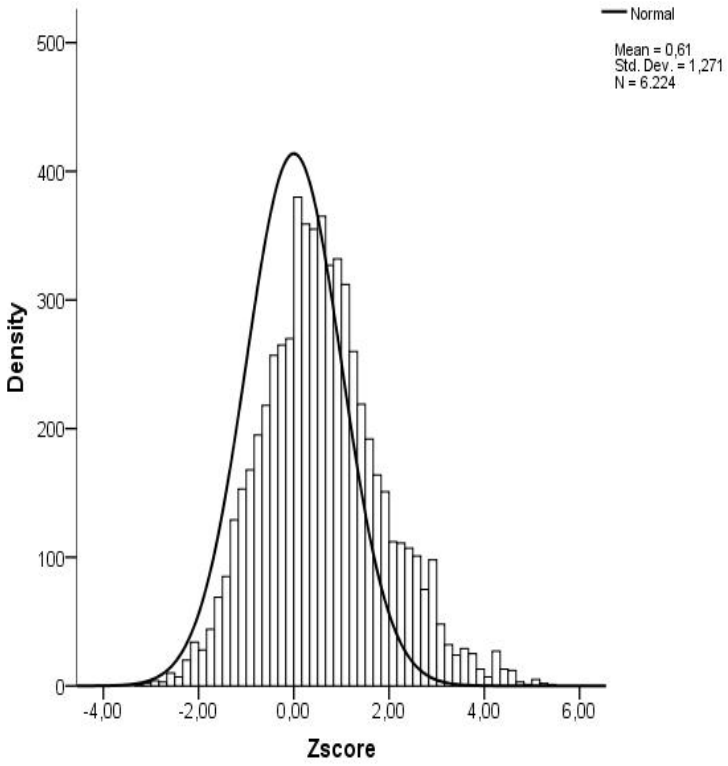
Supplementary Figure 2: Histogram of the absolute meta-analysis z-scores for the replication SNPs in Stage 2; positive/negative z-scores indicate directional consistency/ inconsistency with Stage 1, respectively.



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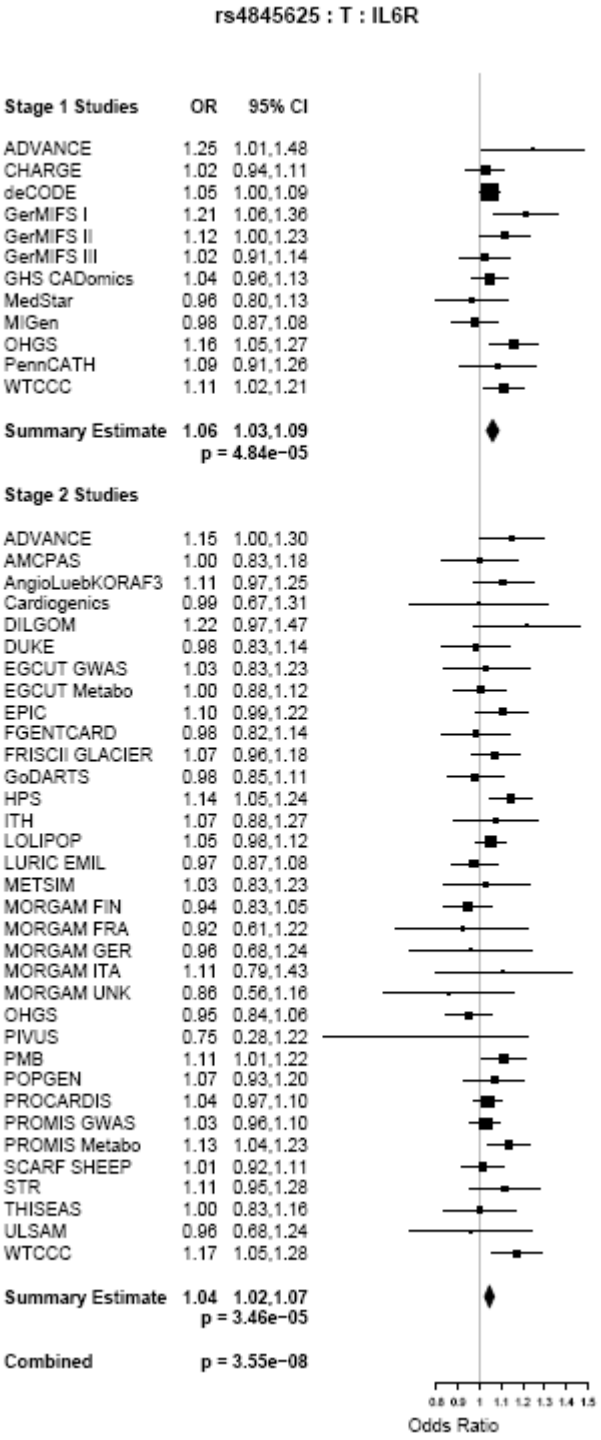
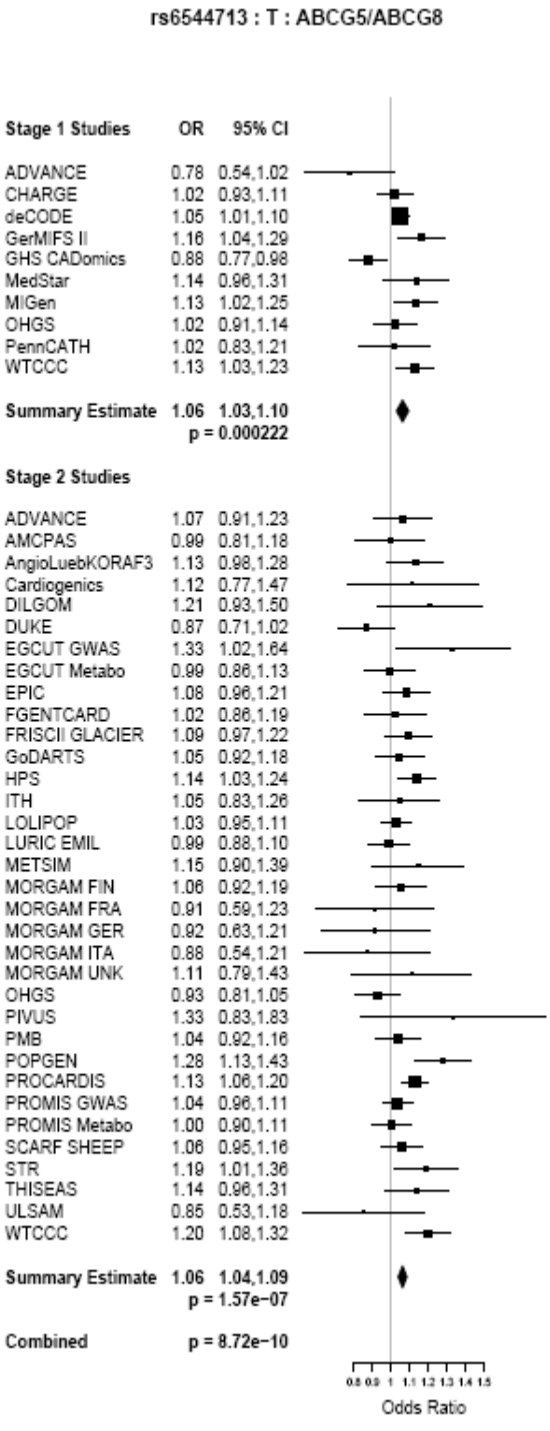
Supplementary Figure 3: Forest plots of the 15 novel coronary disease loci. Single-study boxes and lines indicate odds ratios and 95% confidence intervals. Box sizes are determined by the weight of the study. Explanation of study abbreviations is provided in Supplementary Table 1.





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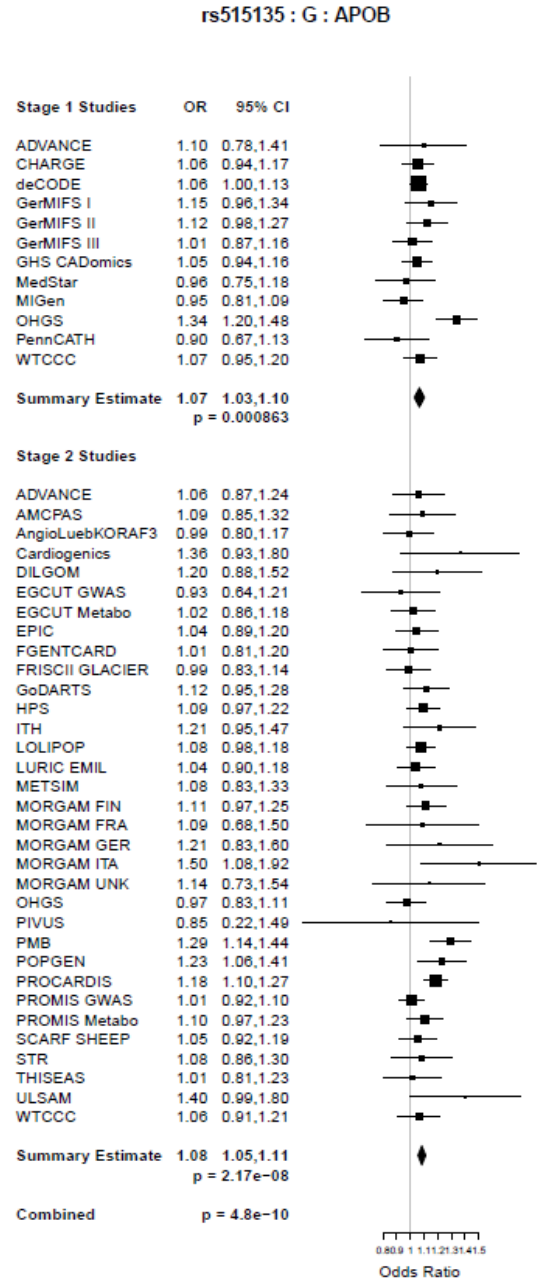

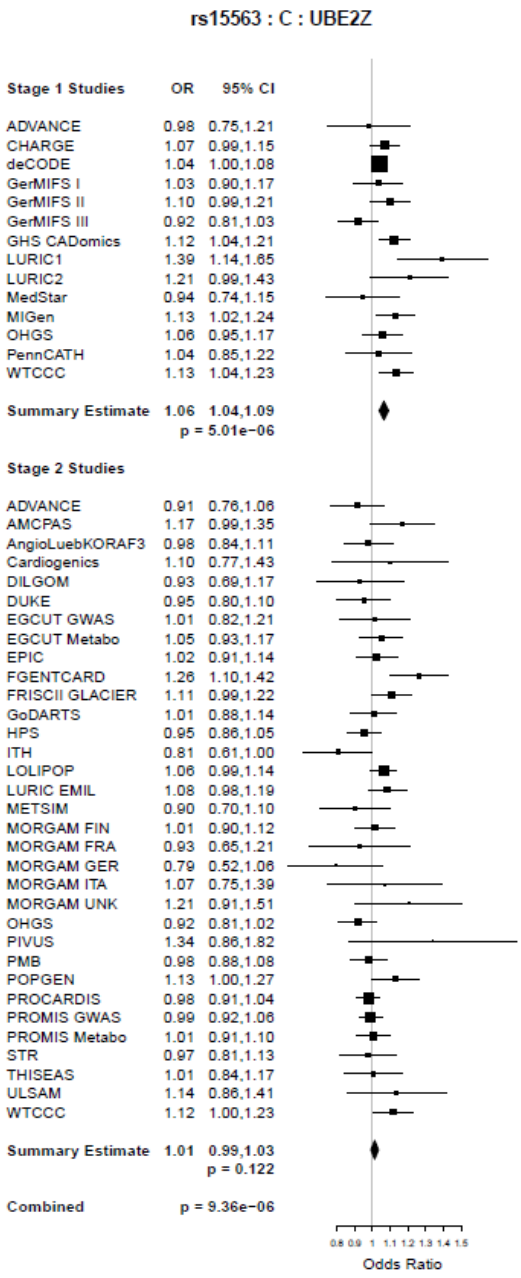

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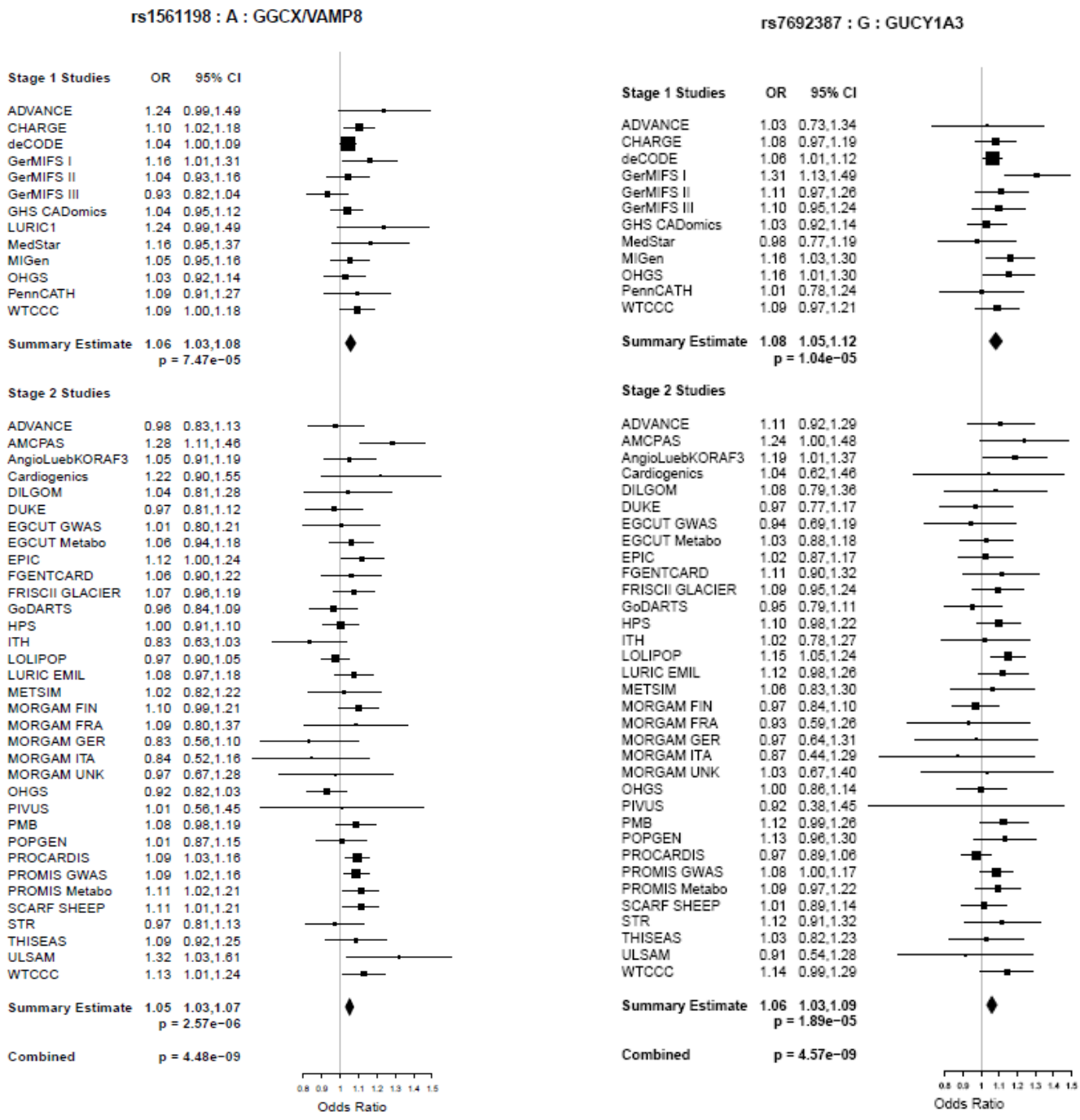

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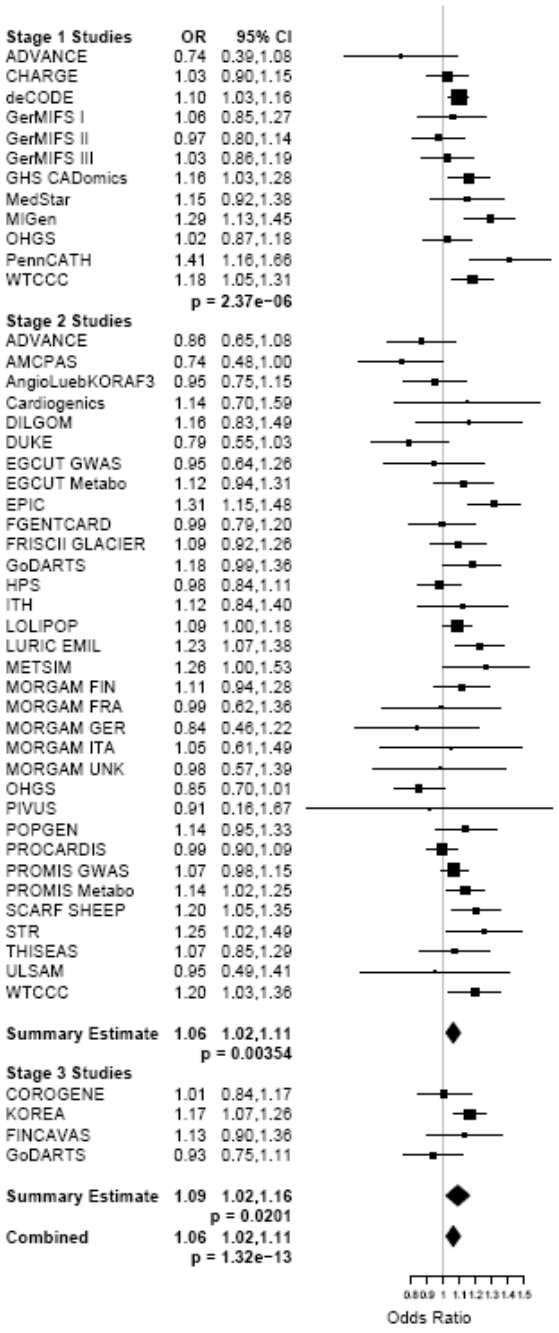

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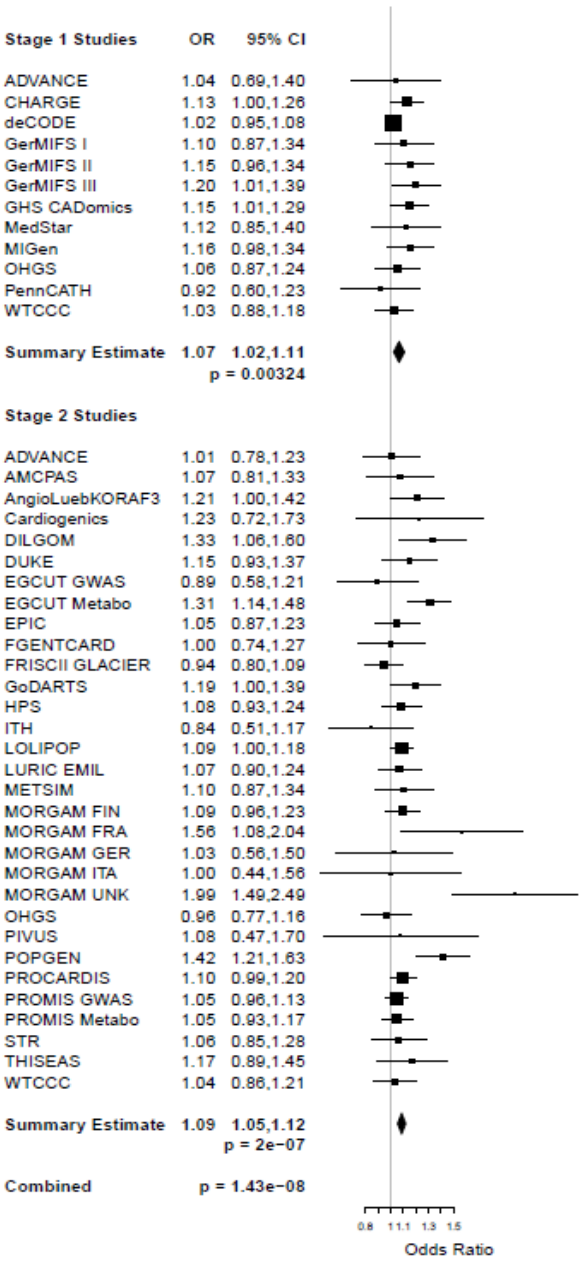

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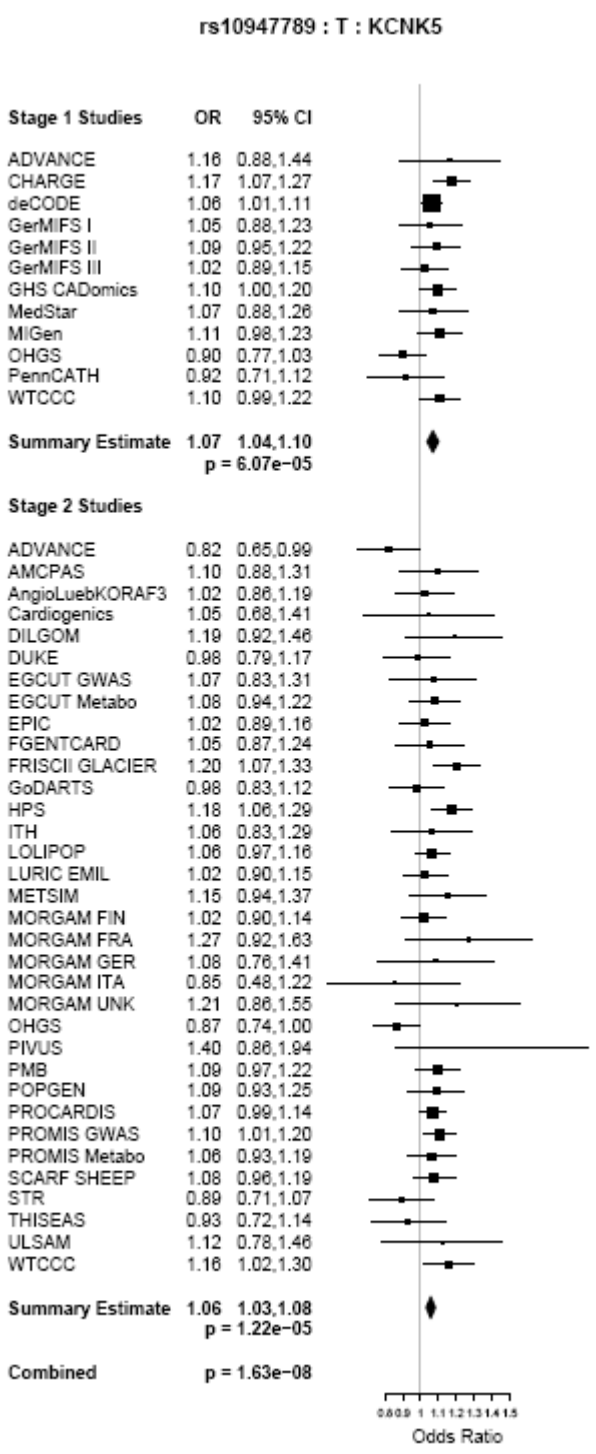

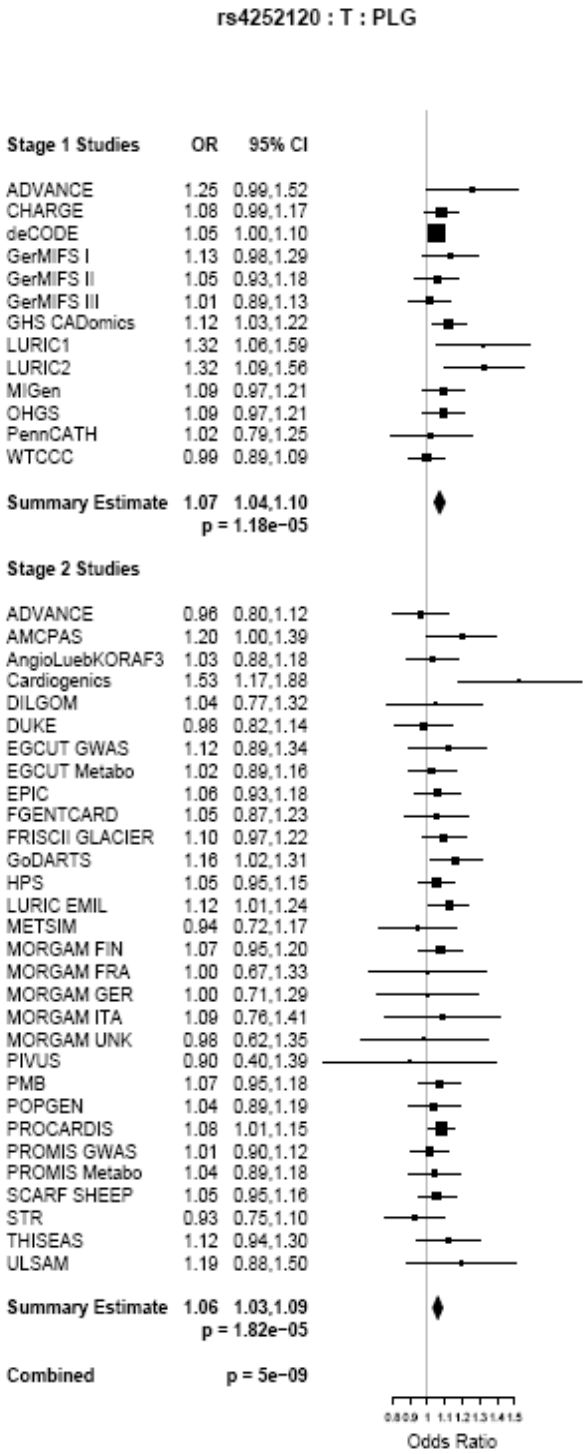

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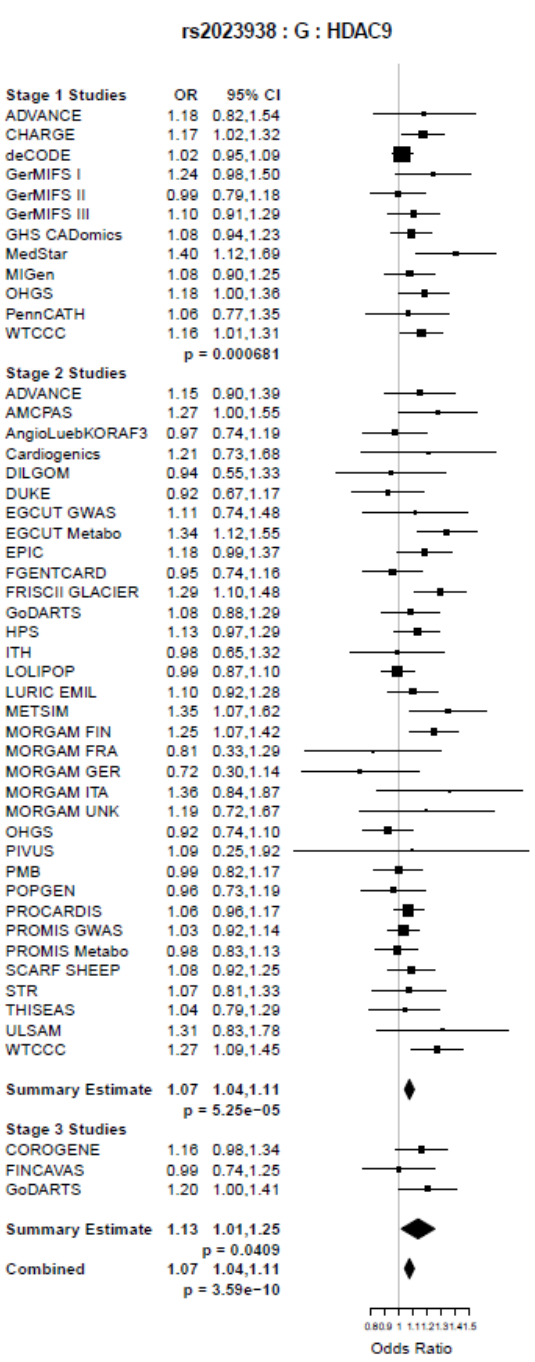

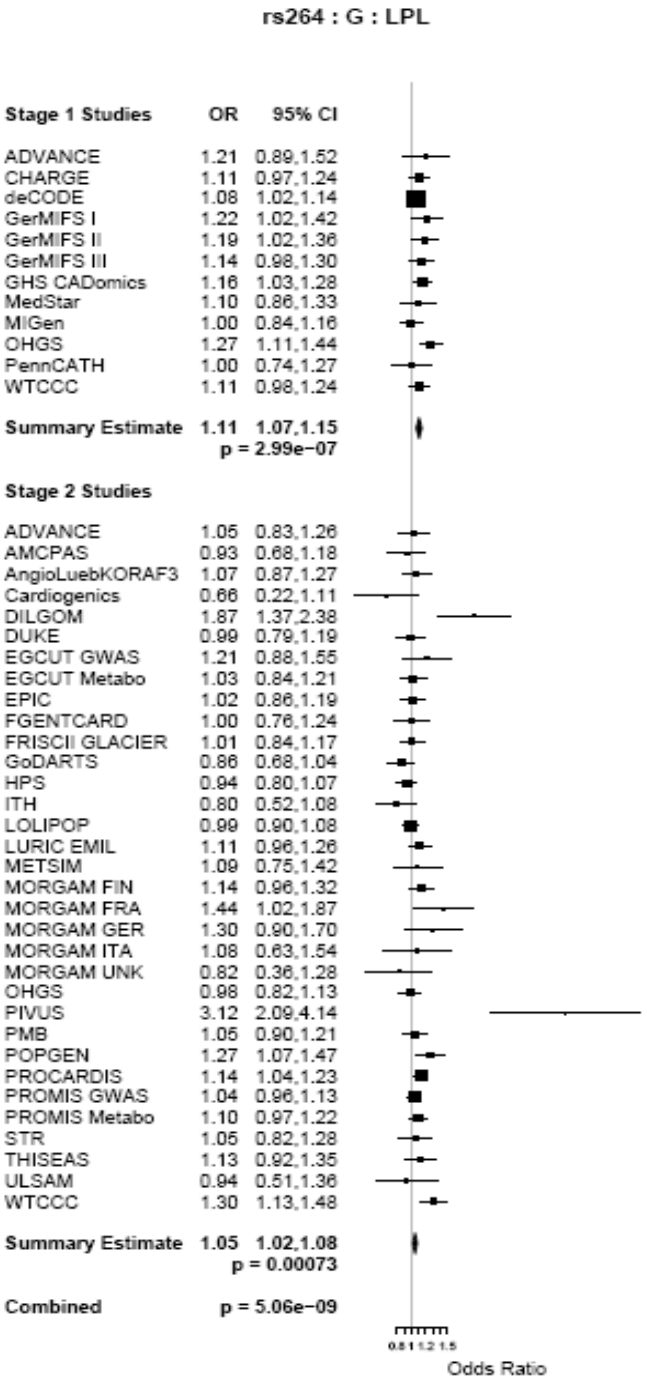

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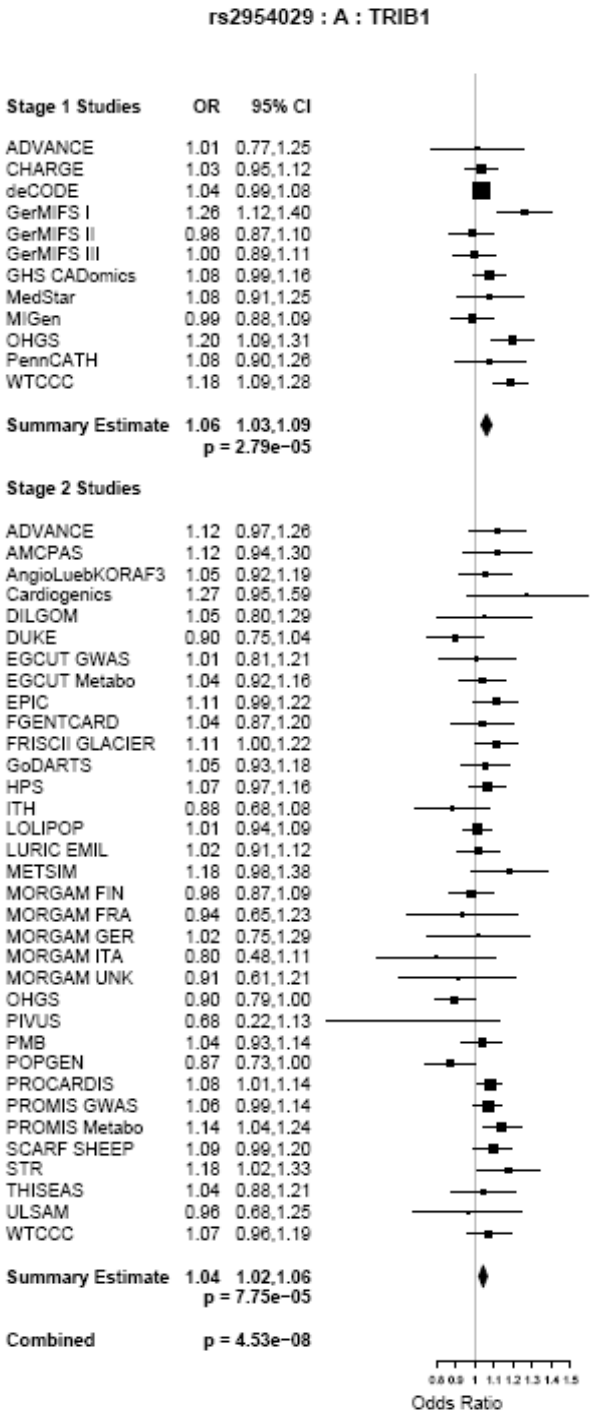

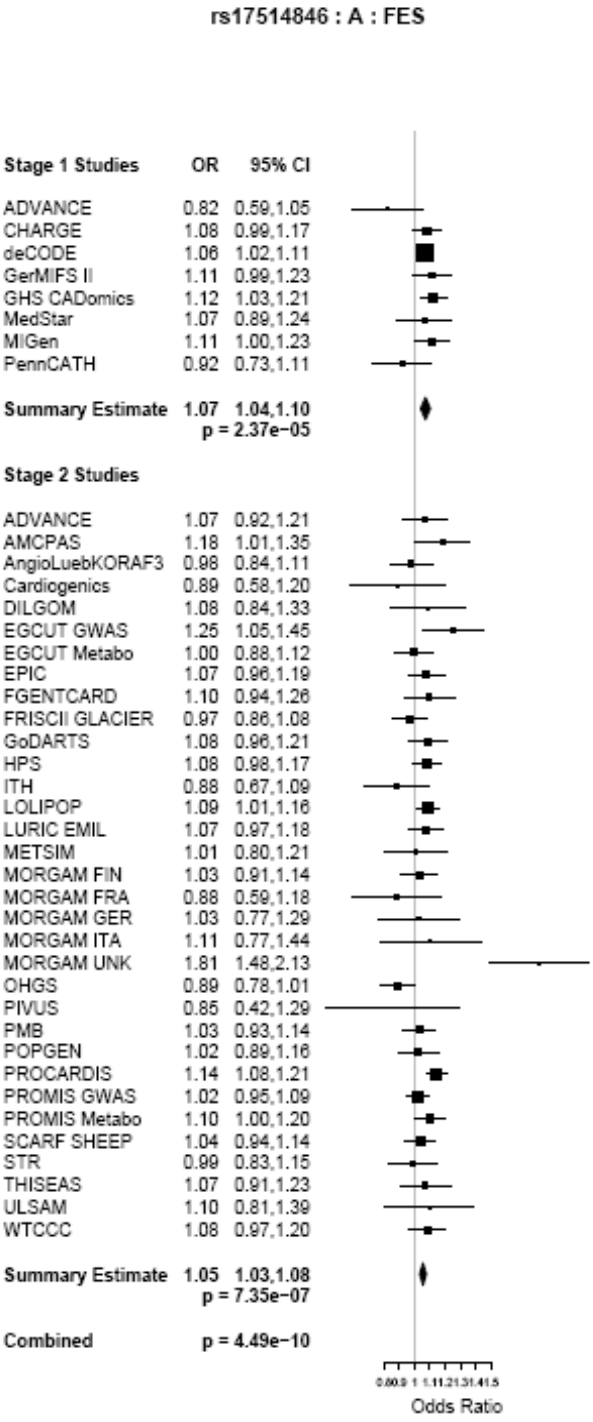

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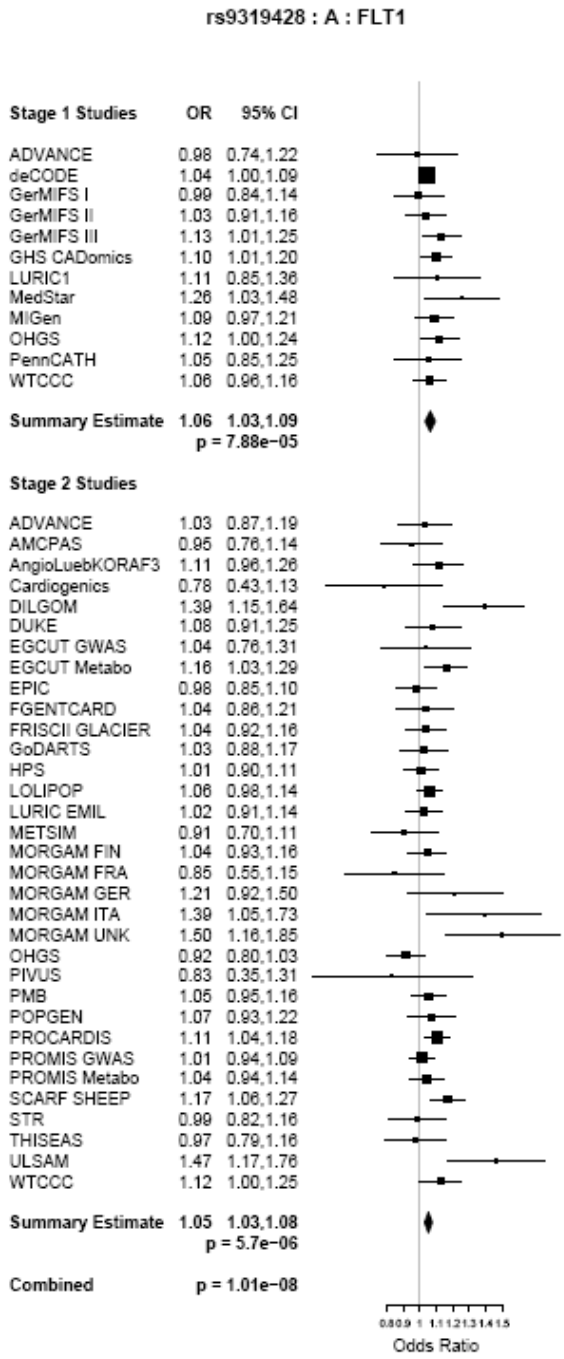

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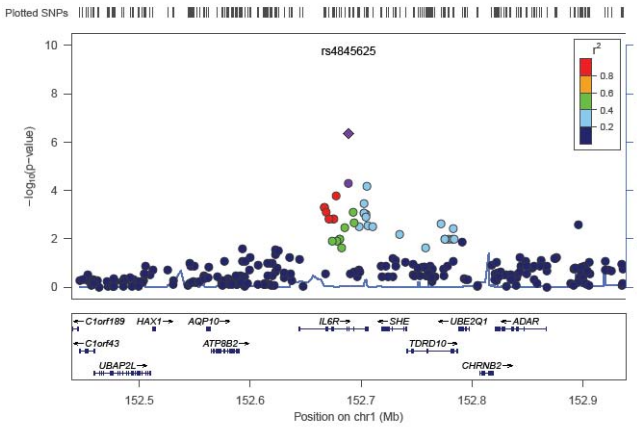
Supplementary Figure 4: Regional associations plots of the 15 novel CAD loci as well as the locus from the young cases vs. controls subgroup analysis. Each circle represents a SNP from the Stage 1 results; purple diamond is the lead SNP from the Stage 1 and 2 combined analysis; purple circle is the identical lead SNP from the Stage 1 results.

IL6R



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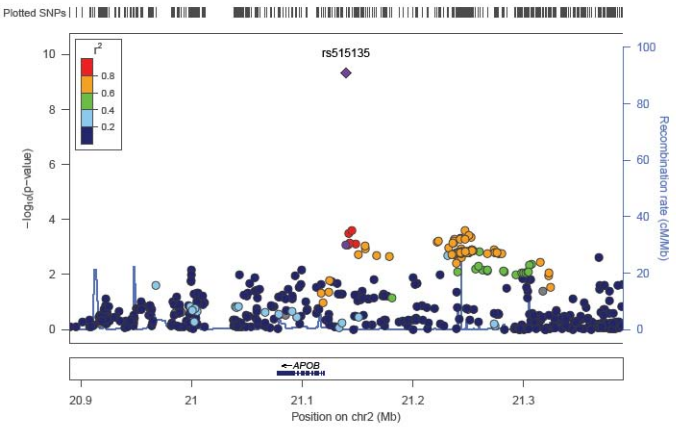
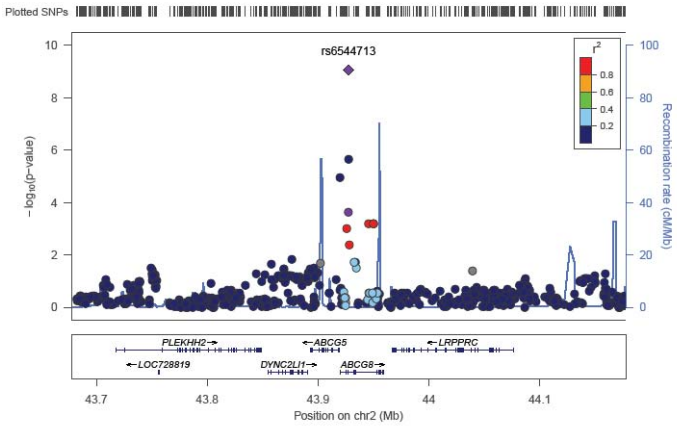


ABCG5/ABCG8



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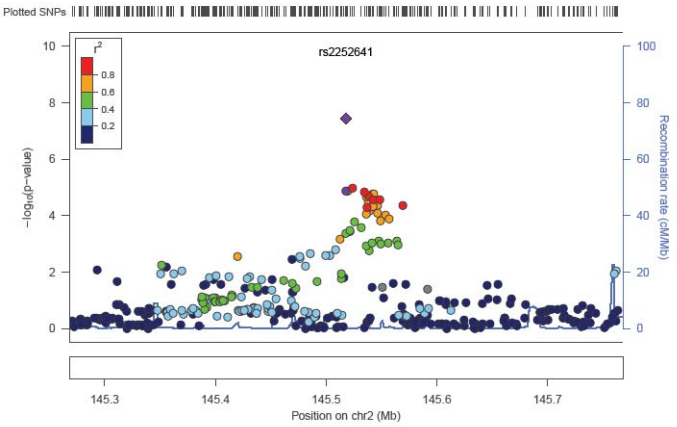

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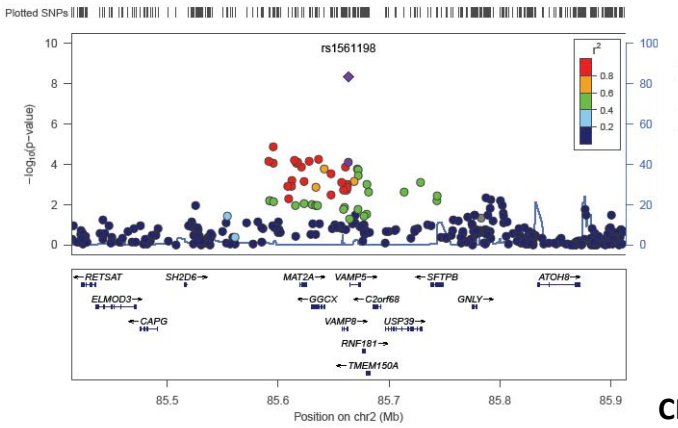
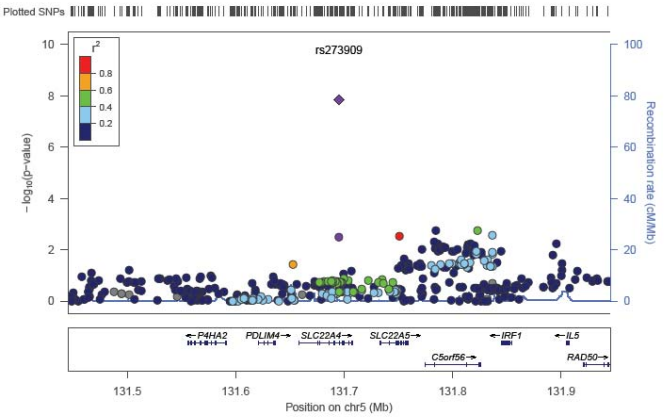
SLC22A4/SLC22A5

GGCX/VAMP8

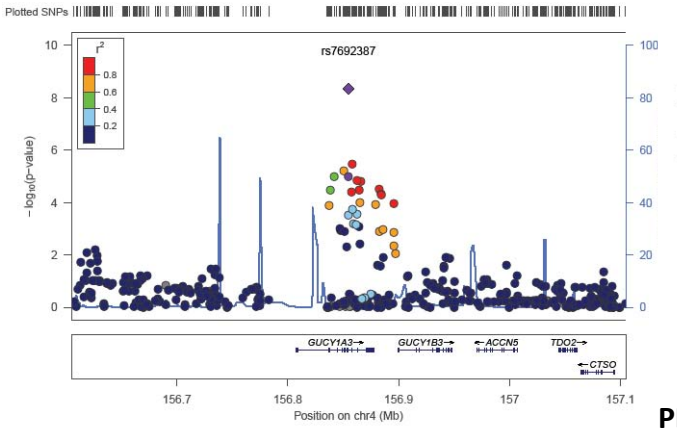


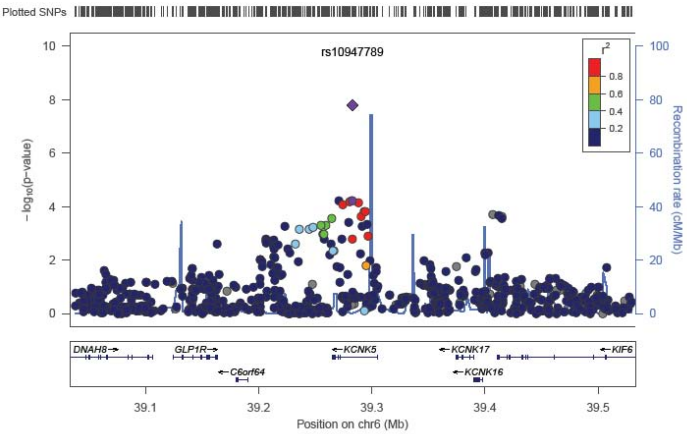


K

CNK5

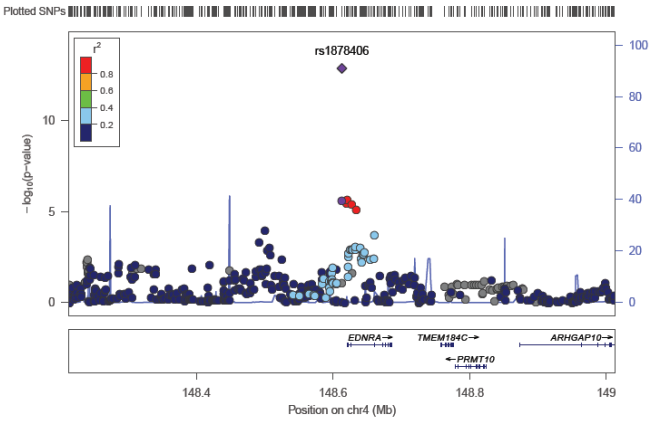
GUCY1A3

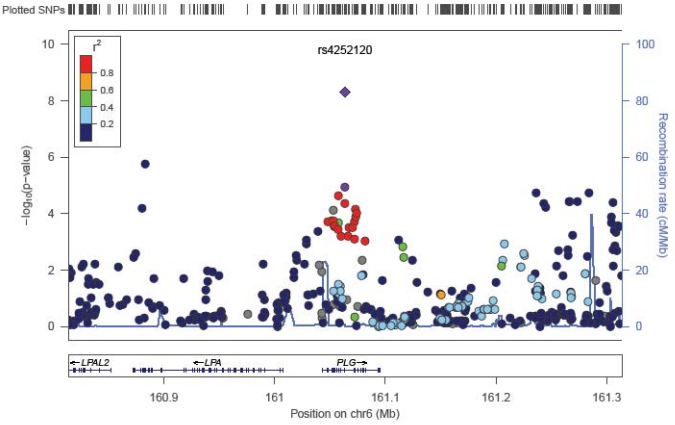




PLG

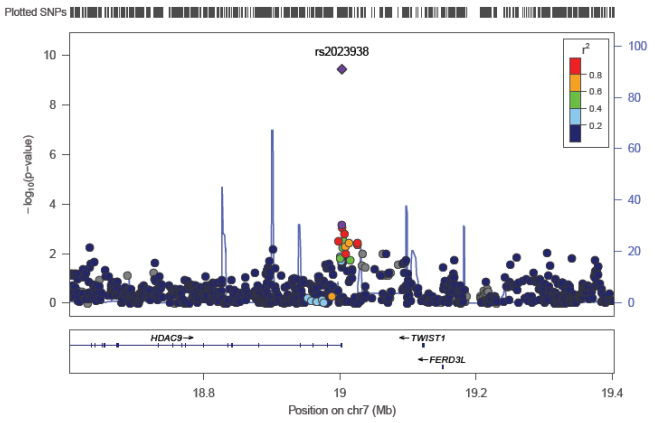
EDNRA



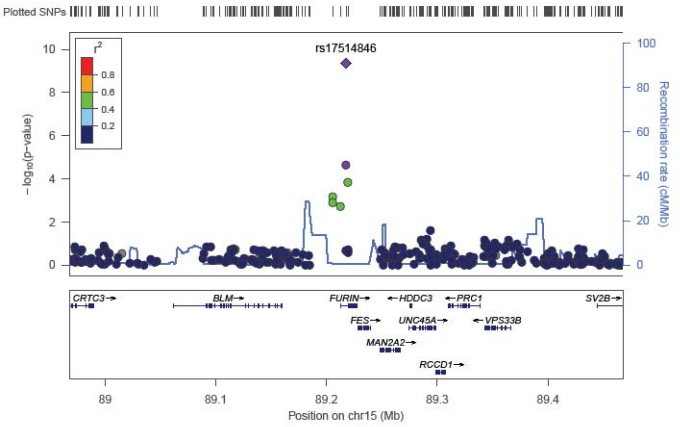


HDAC9

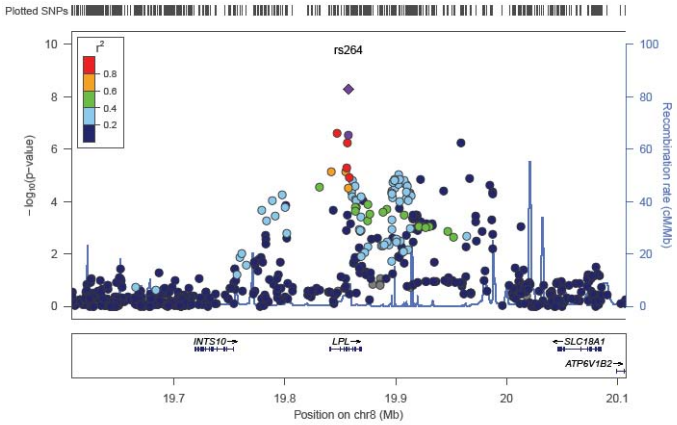
Nature Genetics: doi:10.1038/ng.2480



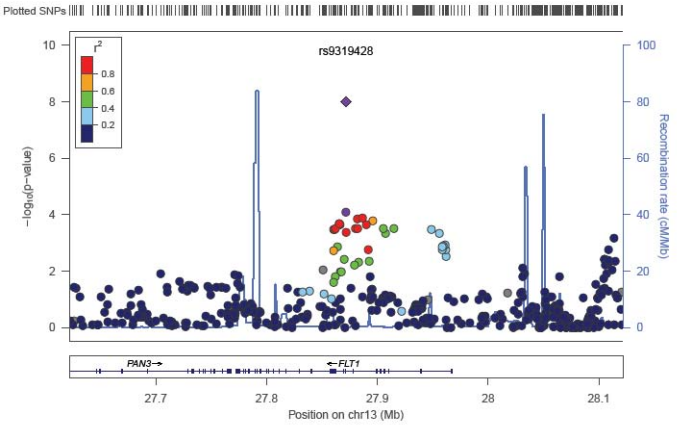
LPL



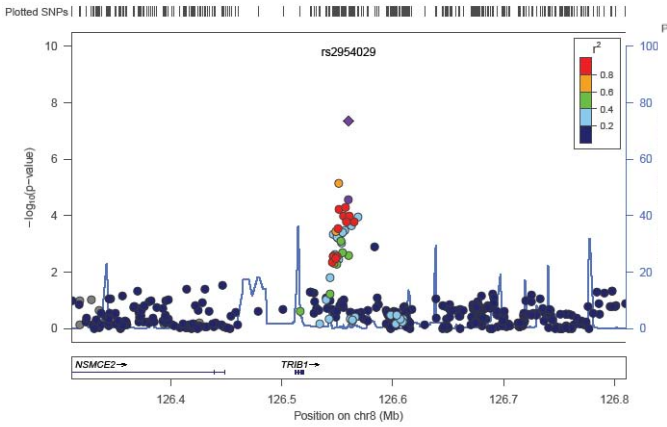
FLT1

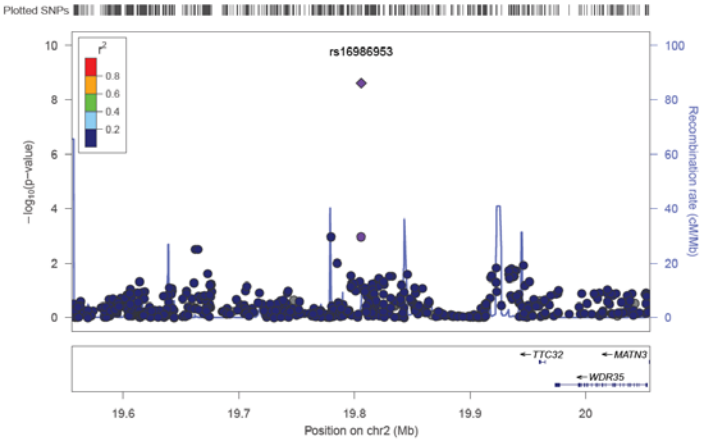


TRIB1



rs16986953

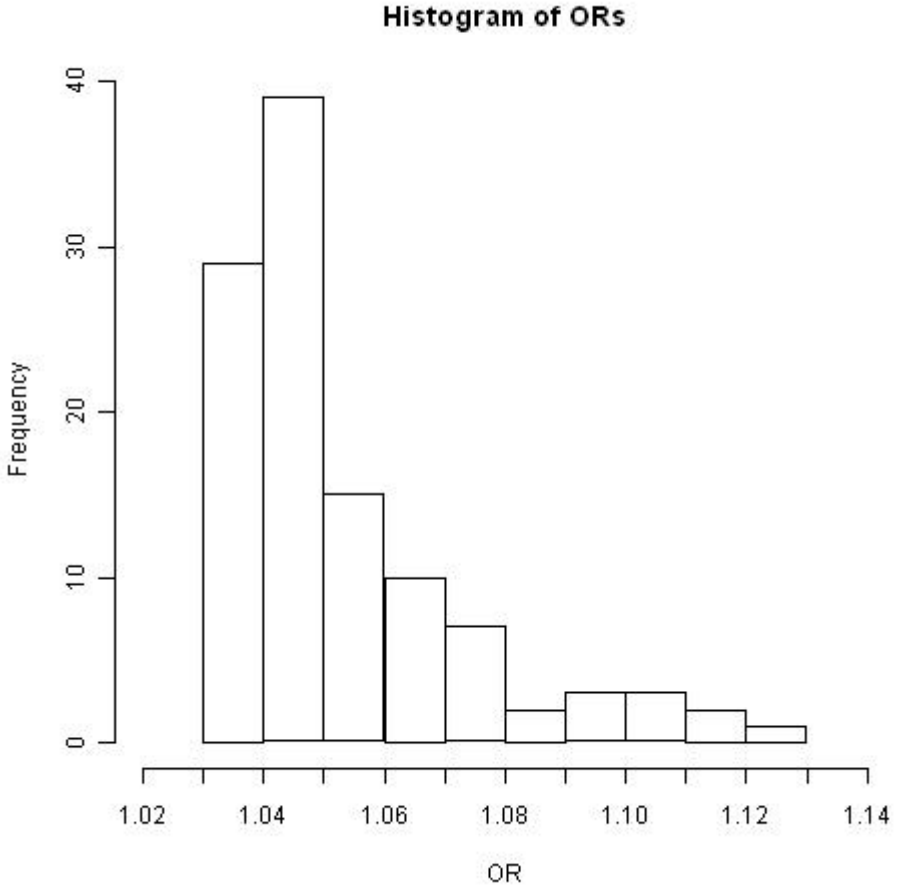




FURIN/FES

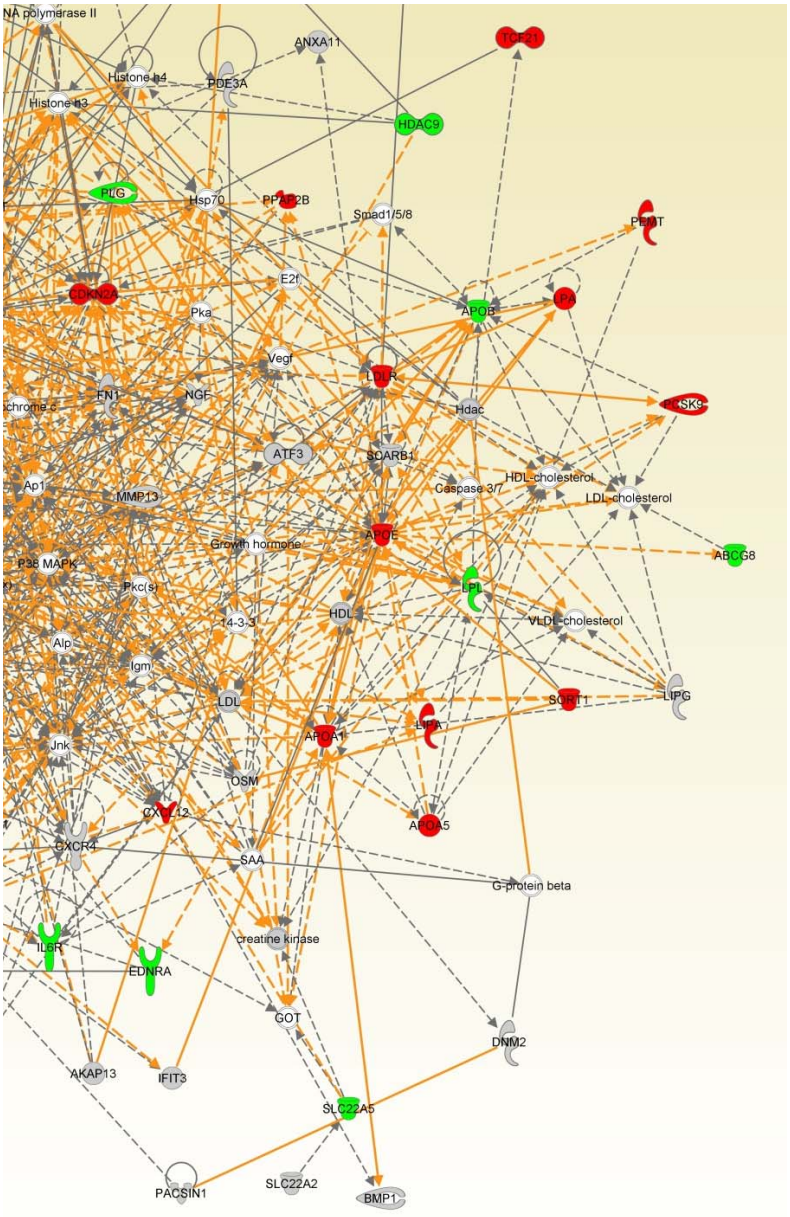
Nature Genetics: doi:10.1038/ng.2480

Supplementary Figure 5: Histogram of ORs for the 104 SNPs (LD threshold of $r^2 < 0.2$ and FDR ≤ 5%); SNPs reported in Table 1 and 2 were excluded. The summary descriptive for these ORs are: mean 1.054, SD 0.0197, SEM 0.00187, median 1.047, IQR 0.0199, min 1.031, max 1.126.



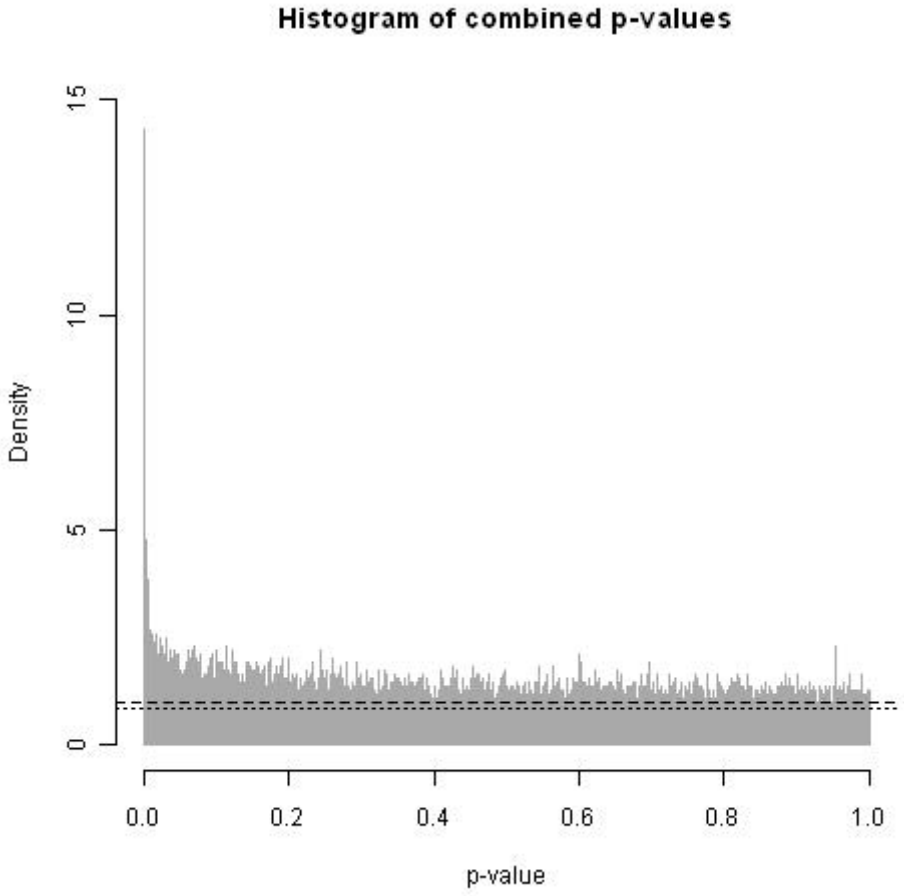
Nature Genetics: doi:10.1038/ng.2480

Supplementary Figure 6: Diagram depicting part of overlapping network ON1 and the interactions recorded in the Ingenuity Knowledge data base between constituent genes. Genes in confirmed CAD loci are marked in red (known) and green (novel) whereas genes selected at FDR 10% are marked in grey. Genes drawn in to the network as neighbours are marked in white. The candidate CAD risk genes shown map to canonical pathways involved in both lipid metabolism and inflammation.



Nature Genetics: doi:10.1038/ng.2480

Supplementary Figure 7: Density histogram of p2_final for the 54,803 SNPs considered in the FDR analysis. The dashed line is the expected distribution if all SNPs were null, the dotted line indicates the $\hat{\pi}_0$ estimate (=0.831).



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Tables

Supplementary Table 1a: Description of studies in Stage2

Study	Phenotype	Sample size	Age(years) Mean(SD)	BMI(kg/m^2) Mean(SD)	Sample size					
					MI	Young CAD	Old CAD	Diabetes mellitus	Diagnosed hypertension	Current smokers
		Total study male/female cases/controls			Total study male/female			Total study cases/controls		
ADVANCE	CAD/Mi	1568 1099/469 900/668	64.0(6.5) 63.2(7.0)/66.0(4.8) 62.7(8.0)/65.8(2.9)	28.8(5.2) 28.9(6.7)/28.5(6.3) 29.1(5.2)/28.3(5.2)	600 457/143	60 59/1	840 619/221	237 157/80	1094 824/270	967 569/398
AMC-PAS	CAD/MI	1608 1104/504 446/1162	48.4(11.4) 49.3(10.9)/46.2(12.1) 41.6(6.0)/51.0(11.8)	NA	354 266/88	440 336/104	6 4/2	NA	NA	NA
Angio-Lueb /KORAF3	CAD	2658 1655/1003 1254/1404	53.0(10.6) 53.4(9.9)/52.3(11.7) 55.0(6.8)/51.1(12.9)	27.7(4.9) 28.1(4.4)/26.9(5.5) 28.4(5.0)/27.0(4.7)*	NA	252 195/57	1003 803/200	NA 284/NA*	1486 947/539*	1533 722/811*
Cardiogenics	CAD/MI	776 492/284 384/392	55.2(8.1) 55.8(8.3)/54.3(7.6) 57.0(8.8)/53.5(7.0)	27.1(4.3) 27.7(4.1)/26.0(4.4) 28.4(4.4)/25.7(3.7)	53 47/6	76 70/6	308 262/46	NA	NA	37 11/26
DILGOM	CAD/MI	3991 1820/2171 147/3844	52.1(13.6) 53.0(13.5)/51.4(13.6) 56.6(9.5)/51.7(13.6)	NA	88 69/19	34 29/5	113 87/26	352 51/301	2192 112/2080	690 20/670
DUKE	CAD/MI	1848 1105/743 1200/648	5.7(9.9) 5.7(9.8)/6.2(9.2) 5.7(9.7)/6.3(8.7)	28.9(6.6) 29.2(6.4)/28.5(6.9) 29.2(6.3)/28.4(7.2)	577 457/120	304 256/48	896 577/319	NA	NA	NA
EGCUT GWAS	CAD/MI	2826 1168/1635 313/2513	45.9(20.8) 39.4(16.2)/50.6(22.4) 69.8(13.8)/43.0(19.6)	26.1(6.6) 26.1(7.6)/26.1(5.8) 28.4(5.0)/25.8(6.7)	39 23/16	21 15/6	281 75/206	139 47/92	733 213/520	453 25/428
EGCUT Metabochip	CAD/MI	2626 1039/1587 983/1643	58.2(11.8) 58.6(11.1)/58.0(12.3) 61.7(10.8)/56.2(11.8)	28.2(6.5) 28.0(5.7)/28.3(6.9) 30.1(6.7)/26.9(6.7)	228 148/80	122 77/45	861 400/461	934 301/633	901 469/432	617 186/431
EPIC	CAD/MI	3935 2069/1866 1526/2409	64.7(10.5) 65.6(10.2)/63.7(10.8) 71.8(8.18)/60.3(9.3)	27.0(4.2) 27.0(3.6)/26.9(4.8) 27.1(3.8)/26.9(4.4)	1526 990/536	7 6/1	1519 984/535	NA	NA	NA
FGENTCARD	CAD/MI	1988 433/1554 1435/553	61.9(11.4) 60.3(11.6)/63.2(10.7) 61.0(11.1)/55.6(11.6)	29.1(4.7) 28.6(4.6)/30.5(6.0) 29.1(5.0)/29.6(5.5)	796 614/182	733 548/185	3910 2762/1148	1992 1787/205	3895 3306/589	2610 2189/421
FRISCII-GLACIER	CAD/MI	9247 4640/4607 2937/6310	55.5(12.0) 57.5(11.8)/53.5(11.9) 66.2(9.8)/50.5(9.3)	NA	1074 792/282	191 177/14	2746 1883/863	NA	NA	NA
GLACIER***	Control	5875 2291/3584	49.4(8.8) 49.9(8.4)/49.2(8.2)	25.8(4.0) 25.9(3.4)/25.7(4.0)	NA	NA	NA	0	1980	1342
GoDARTS	CAD/MI	2765 1634/1131 619/2146	61.7(9.8) 61.2(9.7)/62.5(9.7) 61.5(10.5)/61.8(9.5)	31.8(6.3) 31.0(5.5)/33.0(7.1) 30.0(5.7)/32.3(6.3)	516 366/150	81 63/18	538 377/161	1188 250/938	1227 319/908	1789 338/1451

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HPS	CAD/MI	5457 3069/2388 2700/2757	54.8(13.2) 55.5(11.4)/53.8(15.2) 59.3(8.5)/50.3(15.4)	27.5(4.2) 27.3(3.9)/28.3(5.2)**	1754 1490/264	370 314/56	NA	375**	1171**	376**
ITH	CAD/MI	815 562/253 388/427	63.8(10.5) 63.2(10.6)/65.2(10.1) 63.3(10.6)/64.3(10.3)	27.2(10.4) 26.7(5.7)/28.3(16.5) 26.6(7.1)/27.7(12.6)	388 273/115	36 30/6	352 243/109	116 70/46	401 207/194	NA
LOLIPOP	CAD/MI	6557 5527/1030 2797/3760	55.4(10.6) 55.1(10.7)/56.8(10.0) 59.3(9.7)/52.4(10.2)	27.1(4.3) 26.8(4.1)/28.7(5.3) 27.6(4.5)/26.8(4.2)	1228 1122/106	493 427/66	2304 1862/442	1782 1122/660	4090 2186/1904	623 236/387
LURIC-EMIL	CAD/MI	4560 2769/1791 2068/2492	56.4(13.6) 57.1(13.1)/55.3(14.3) 58.9(13.0)/49.4(12.9)	NA	1230 964/266	210 172/38	1858 1386/472	NA	NA	NA
METSIM	CAD/MI	2119 2119/0 224/1895	59.4(7.4) 59.4(7.4)/NA(NA) 64.6(6.3)/58.7(7.3)	28.5(4.8) 28.5(4.8)/NA(NA) 30.2(6.4)/28.3(4.5)	109 109/0	35 35/0	168 168/0	99 18/81	NA	19 1/18
MORGAM-FIN	CAD	2484 2118/366 1242/1242	62.7(7.74) 62.6(7.7)/63.0(8.2) 64.5(7.3)/60.9(7.8)	27.7(4.4) 27.5(4.2)/28.8(5.1) 28.1(4.3)/27.3(4.3)	32 24/8	NA	1192 1015/177	214 149/65	1473 771/702	1286 644/642
MORGAM-FRA	CAD/MI	366 366/0 183/183	57.0(3.0) 57.0(3.0)/NA(NA) 57.6(3.0)/56.3(2.7)	27.3(3.3) 27.3(3.3)/NA(NA) 27.6(3.2)/27.0(3.5)	50 50/0	NA	183 183/0	24 12/12	202 116/86	101 63/38
MORGAM-GER	CAD/MI	430 340/90 215/215	61.7(8.5) 61.6(8.5)/62.3(8.4) 64.5(7.8)/58.9(8.2)	28.0(4.0) 27.8(3.6)/28.5(5.0) 28.3(4.4)/27.6(3.5)	85 67/18	14 13/1	201 157/44	54 37/17	247 131/116	159 99/60
MORGAM-ITA	CAD/MI	302 242/60 151/151	58.4(9.2) 57.3(9.3)/62.8(7.3) 61.3(9.3)/55.5(8.1)	26.4(3.9) 26.2(3.4)/27.3(5.5) 26.7(4.0)/26.0(3.9)	62 52/10	25 23/2	126 98/28	36 23/13	163 94/69	114 68/46
MORGAM-UNK	CAD/MI	328 328/0 164/164	57.9(4.0) 57.9(4.0)/NA(NA) 59.7(4.1)/56.1(3.0)	26.4(3.4) 26.4(3.4)/NA(NA) 26.9(3.3)/26.0(3.4)	65 65/0	NA	164 164/0	14 9/5	150 87/63	129 74/55
OHGS	CAD/MI	3419 2212/1207 1998/1421	59.6(14.2) 54.5(13.5)/67.2(12.3) 49.0(7.3)/74.5(5.5)	28.1(5.3) 28.5(4.9)/27.4(5.8) 29.1(5.5)/26.7(4.6)	1200 963/237	997 877/120	1001 637/364	72 0/72	1718 1147/571	434 399/35
PIVUS	CAD	978 490/488 94/884	69.7(2.7) 69.3(3.5)/70.1(1.5) 65.0(7.2)/70.2(0.2)	27.1(4.4) 27.1(3.7)/27.1(4.9) 27.7(4.3)/27.0(4.4)	94 74/20	NA	NA	84 16/68	701 73/628	105 15/90
PMB	CAD/MI	5381 2920/2461 922/4459	 57.6(10.7)/58.4(10.1) 59.7(10.8)/57.6(10.3)	 27.5(5.6)/27.4(5.6) 29.1(5.1)/27.1(5.7)	922 542/380	738 386/352	184 156/28	3238 922/2316	501 238/263	491 183/308
PopGEN	CAD	1836 1276/560 865/971	54.1(11.7) 53.8(10.4)/54.9(14.3) 53.5(5.7)/54.7(15.2)	NA	NA	198 160/38	667 554/113	NA	NA	NA
PRO-CARDIS	CAD/MI	12237 6967/5270 5719/6518	57.5(11.6) 56.2(11.1)/59.2(12.1) 53.6(8.1)/60.9(13.1)	28.1(4.5) 28(4.1)/28.2(5.5) 28.5(4.5)/26.4(4.0)	4598 3589/1009	1680 1398/282	4039 2887/1152	925 870/55	1319 961/358	1102 864/238
PROMIS GWAS	CAD/MI	7353 5948/1405 3729/3624	53.8(10.3) 53.4(10.4)/55.3(9.6) 54.2(10.6)/53.5(10.0)	25.3(4.4) 25.1(4.2)/25.9(4.8) 25.2(4.4)/25.4(4.4)	3729 3099/630	1171 1036/135	2558 2063/495	1839 1080/759	2108 1080/1028	2096 1166/930
PROMIS Metabochip	CAD/MI	3625 2965/660 1852/1773	52.5(9.9) 52.1(10.1)/54.0(9.0) 52.9(10.5)/51.9(9.3)	26.1(4.3) 25.9(4.2)/26.7(4.7) 26.0(4.1)/26.1(4.4)	1851 1569/282	648 590/58	1204 979/225	574 363/211	NA	NA
SCARF-SHEEP	CAD/MI	3417 2458/959 1525/1892	58.1(7.3) 57.2(7.1)/60.5(7.2) 57.6(7.3)/50.5(7.0)	26.1(4.8) 26.1(4.5)/25.9(5.4) 26.7(5.1)/25.6(4.4)	1525 1122/403	302 256/52	1223 872/351	341 237/104	1467 658/809	1133 620/513

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STR	CAD	1719 760/959 447/1272	75.6(10.9) 74.4(10.4)/76.5(11.2) 78.9(9.7)/73.1(11.0)	25.0(3.9) 25.0(3.3)/25.0(4.2) 25.5(3.78)/24.9(3.9)	447 253/194	NA	NA	77 30/47	764 249/515	122 36/86
THISEAS	CAD/MI	1506 871/635 508/998	58.7(13.1) 57.2(12.3)/60.8(13.9) 61.1(10.4)/57.5(14.2)	28.7(6.7) 28.7(7.6)/28.5(5.3) 28.3(9.6)/28.8(5.3)	262 216/46	88 79/9	420 347/73	310 140/170	643 256/387	360 161/199
ULSAM	CAD	1175 1175/0 242/933	71.8(5.6) 71.8(5.6)/NA(NA) 72.5(8.7)/71.2(0.4)	26.0(3.2) 26.0(3.2)/NA(NA) 26.7(3.8)/25.9(3.0)	242 242/0	NA	NA	45 18/27	338 75/263	222 50/172
WTCCC CAD2	CAD/MI	5429 3347/2082 1213/4246	 46.7(6.7)/45.2(4.6) 53.5(9.6)/44(0)	 28.1(4.2)/27.0(5.6) 28.7(4.9)/27.4(4.7)	1124 914/210	435 366/69	778 613/165	301 116/185	1560 473/1087	1373 407/966

* Descriptive information only available for some individuals within the cohort
** Descriptive information only available for the cases within the cohort

***Results for the control cohort GLACIER presented separately, Total and Male/Female data descriptives.

Supplementary Table 1b: Description of studies in Stage3

					Sample size					
		Sample size	Age(years) Mean(SD)	BMI(kg/m^2) Mean(SD)	MI	Young CAD	Old CAD	Diabetes mellitus	Diagnosed hypertension	Current smokers
Study	Phenotype		Total study male/female cases/controls			Total study male/female			Total study cases/controls	
COROGENE	CAD	3208 2079/1129 2000/1208	62.72 (12.48) 61.25(12.53)/65.44 (11.93) 66.0 (11.8) / 56.74 (11.29)	27.32 (4.59) 27.49(4.25)/27.02(5.14) 27.51(4.72)/27.02(4.34)	200 172/28	178 155/23	1822 1244/578	468 397/71	2075 1374/701	978 659/319
FINCAVAS	CAD/MI	1489 997/492 798/691	58.1 (10.7) 57.8 (10.6)/58.6 (10.9) 60.0 (10.2)/55.8 (10.8)	27.7 (4.6) 27.7 (4.3)/27.6 (5.0) 27.9 (4.5)/27.5 (4.6)	99 85/14	128 107/21	670 518/152	184 116/68	NA	373 222/151
GenRIC	CAD/MI	4789 2935,1854 2099,2690	52.8 (8.1) 51.8 (8.4)/ 54.4 (7.5) 51.7 (7.5)/ 53.7 (8.5)	24.6 (3.0) 24.7 (2.9)/ 24.3 (3.1) 25.3 (3.0)/ 24.0 (2.8)]	680 521/ 159	792 716/ 76	1,307 568/ 739	653 449/ 204	None	1,154 653/ 501

[2] Illumina Cardio-Metabochip

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Supplementary Table 2a: General Study Characteristics for Stage 2 studies

Study	Full Study name	Reference	Ethnicity	Region of recruitment	Phenotype	Phenotype definition	Control definition
ADVANCE	Atherosclerotic Disease, VAscular FuNction, & GenetiC Epidemiology study	16490908 16840522 17084253 18443000	European	Northern California, USA	CAD/MI	Kaiser Permanente of Northern California (KPNC) Medical Care Program members aged 45 years or older for males and 55 years or older for females at the time of their incident clinical coronary artery disease event between 28 October 2001 and 31 December 2003. For MI, patients had to have positive cardiac enzymes in the electronic databases as well as a primary discharge diagnosis of myocardial infarction (ICD 9 code 410). For stable angina, patients had to have diagnosis of stable angina (ICD9 code 413.x) in the electronic outpatient databases followed by confirmation from both the primary care physician and the patient of the recent onsent of incident stable and typical angina. Two cases from the early onset CAD cohort (age of onset of CAD < 45 years for men and < 55 years for women) not included in prior ADVANCE GWAS were also genotyped.	Members of the KPNC Medical Care Program aged 60 to 69 as of January 6, 2001, with no history of cardiovascular disease, cancer (other than nonmelanoma skin cancer), renal failure, liver cirrhosis, dementia, or human immunodeficiency virus/ acquired immunodeficiency syndrome or with a source of care greater than 50 miles (80.47 km) from the clinic used for data collection were recruited.
AMC-PAS	The Academic Medical Center Amsterdam Premature Atherosclerosis Study	19164808	European	The Netherlands	CAD/MI	Symptomatic CAD before the age of 51 years, defined as MI, coronary revascularization, or evidence of at least 70% stenosis in a major epicardial artery	Blood donors from the north-west region of the Netherlands; recruited at routine Sanquin Blood Bank donation sessions. More than 95% of the controls are from the same region as the cases of the AMC-PAS cohort.
Angio-Lueb/ KORA F3	Lübeck Registry of Structural Heart Disease /KORA (Kooperative Gesundheitsforschung	21378990 16648850	European	Germany	CAD/MI	Consecutive patients referred for coronary angiography, classified as CAD/MI cases based on the coronary angiogram; CAD < 65 y in males, CAD < 70 y in females	Population based controls conducted between 1994 and 2004

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	in der Region Augsburg) survey S3/F3						
Cardiogenics	Cardiogenics Study	17634449	European	France, Germany, England	CAD/MI	Patients from Germany and England were under the age of 65 with a confirmed primary MI within the preceding 3-36 months. Exclusion criteria were (*i*) a history of diabetes mellitus based on plasma glucose >7.0 mmol/l or HbA1C > 7.0 (*ii*) renal insufficiency, (*iii*) patients not on statin therapy, (*iv*) CRP level >10mg/dl, (v) patients not fasting at the time of blood sampling or (*vi*) current smokers. The Paris cohort comprised patients aged 33 to 87, recruited within the BAAAC (Banque d'ADN et d'ARN de patients présentant une Athérosclérose Coronarienne) study. with symptoms of acute coronary syndrome who had one stenosis >50% diagnosed in at least one major coronary artery.	Healthy individuals (aged 32 to 65 years) recruited in Cambridge who were blood donors recruited as part of the Cambridge Bioresource.
DILGOM	The Dietary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome study	21179014	European	Finland	CAD/MI	All CAD: Incident definite or possible MI or coronary death, or unstable angina during follow-up, Coronary revascularization during follow-up, Documented MI at baseline, or an unclassifiable coronary death during follow-up. MI:Definite myocardial infarction.	Non-cases from the same population-based longitudinal cohort study
DUKE	The Duke Cathgen Study	20173117	European	United States	CAD/MI	Cases had at least one epicardial coronary vessel with at least 50% blockage. Age of onset was no older than 65 for women and 55 for men. Subjects (case and control), were excluded if they had severe pulmonary hypertension or congenital heart disease or were diabetic.	Controls were required to have no epicardial coronary vessel with greater than 30% blockage. Controls with a history of ICC/PCI, CABG, MI or transplant were excluded. Controls were required to be at least 50 years old.
EGCUT*	Estonian Genome Center of University of Tartu	19424496	European	Estonia	CAD/MI	Cases were study participants who reported following cardiovascular disease events (ICD10 I20-I26) when recruited.	Controls were study participants who didn't report following cardiovascular disease events (ICD10 I20-

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							I26) when recruited.
EPIC	The European Prospective Investigation into Cancer		European	England	CAD/MI	Cases were individuals who developed a fatal or non-fatal CAD during an average follow-up of 11 years, until June 2006. Participants were identified if they had a hospital admission and/or died with CAD as the underlying cause. CAD was defined as cause of death codes ICD9 410-414 or ICD10 I20-I25, and hospital discharge codes ICD10 I20.0, I21, I22 or I23 according to the International Classification of Diseases, 9th and 10th revisions.	Controls were study participants who remained free of any cardiovascular disease during follow-up (defined as ICD9 401-448 and ICD10 I10-I79). Controls were matched to each case by sex, age (within 5 years), and time of enrolment (within 3 months).
FGENTCARD	Functional Genomic Diagnostic Tools for Coronary Artery Disease	In preparation	European	Lebanon	CAD/MI	The study subjects consisted of 6517 individuals who underwent cardiac catheterization following a single consistent and stringent recruitment protocol between August, 2007 and March 2011 at several hospitals in Lebanon. Catheterization was prompted for myocardial infarction (MI) (12.5%) as diagnosed by electrocardiogram and high troponin levels, unstable angina (27.5%), or other reasons, such as stable angina, or heart failure, or reversible ischemia by stress testing (59.9%). All patients underwent coronary catheterization by Judkins technique. The four main coronary arteries: the left main artery (LMCA), the left anterior descending artery (LAD), the left circumflex artery (LCx), and the right coronary artery (RCA) were visualized from different angles by angiography. The extent of stenosis in these vessels was assessed and recorded by percentage. Cases were defined as follows: Mildly diseased if at least one of the four vessels has less than 50% stenosis, severly diseased if any of the four vessels has ≥50% setnosis.	Controls are subjects with no stenosis in the 4 main vessels .
FRISCII	Fragmin and Fast Revascularization	10475181	European	Sweden, Norway and	CAD/MI	FRISCII patients were eligible for inclusion if they had symptoms of	The GLACIER cohort was used in these analyses as a

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	during Instability in Coronary Artery Disease (FRISCII)			Denmark			
GLACIER	Gene x Lifestyle interactions And Complex traits Involved in Elevated disease Risk (GLACIER)	20870969	European	Sweden	Control	ischaemia that were increasing or occurring at rest, or that warranted the suspicion of acute myocardial infarction, with the last episode within 48 h before the start of dalteparin or standard heparin treatment. Myocardial ischaemia had to be verified by electrocardiography (ST depression ≥0·1 mV or T-wave inversion ≥0·1 mV) or by raised biochemical markers (creatine kinase [CK]-MB >6 ug/L, troponin-T >0·10 ug/L, qualitative troponin-T test positive, or catalytic activity of CK, CK-B, or CK MB higher than the local diagnostic limit for myocardial infarction). Exclusion criteria were raised risk of bleeding episodes, anaemia, or indication for or treatment in the past 24 h with thrombolysis, angioplasty in the past 6 months, being on a waiting list for coronary revascularisation, other acute or severe cardiac disease, renal or hepatic insufficiency, known clinically relevant osteoporosis, other severe illness, hypersensitivity to randomised drugs, anticipated difficulties with cooperation or participation in this or another clinical trial. Patients with previous open-heart surgery, advanced age (eg, >75 years), or other disorders that made randomisation to early revascularisation inappropriate.	comparison cohort for FRISCII. GLACIER is a subset of the Västerbottens Intervention Project, a population-based cohort from northern Sweden. The GLACIER cohort is comparable to the full VIP cohort in demographic, anthropometric, and lifestyle characteristics.
GoDARTS	The Genetics of Diabetes Audit and Research in Tayside Scotland	9329309	European	Scotland	CAD/MI	First-ever CAD event. Defined as fatal and non-fatal myocardial infarction, unstable angina or coronary revascularisation	Controls were free of coronary artery disease, stroke and peripheral vascular disease.
HPS	MRC/BHF Heart Protection Study	15016485	European	UK	CAD/MI	History of MI, unstable or stable angina, coronary artery bypass grafting, or angioplasty	Population controls were used from the UK Twins Study and WTCCC2 National Blood Service collections
ITH	The INTERHEART Study	20031563	European	Worldwide	CAD/MI	Incident acute MI, presenting to a hospital within 24 hours of symptom	Age and sex matched hospital and community based, with no

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						onset	previous diagnosis of heart disease or history of exertional chest pain
LOLIPOP	London Life Sciences Population study	18193046, 18454146, 19820698	South Asian	UK West London	CAD/MI	CAD was defined as a history of MI or coronary artery revascularization (CABG or PCI), or angiographically confirmed coronary artery stenosis greater than 50%. Clinical diagnosis of MI is based on two out of three of: 1. Chest pain, 2. Raised cardiac enzymes, 3. ECG changes.	Indian Asian men and women from the same cohort (aged 35 - 75 yrs), without diagnosis or history of CAD.
LURIC-EMIL	LUdwigshafen RIsk and Cardiovascular health study and Echinococcus Multilocularis and Internal Diseases in Leutkirch study	20065167 16981990	European	Germany	CAD/MI	Angiographically confirmed CAD (at least one coronary vessel with a stenosis > 50%) were included	GerBS control series that consists of healthy, unrelated blood donors recruited between May-July 2004 from the southwestern area of Germany / EMIL controls include population-based non-cases subjects
METSIM	METabolic Syndrome In Men	19223598	European	Kuopio, Finland	CAD/MI	CAD cases: Angiography-confirmed CAD, myocardial infarction, balloon angioplasty or coronary bypass	Controls were selected from the same population-based sample and were free from MI, coronary angiography, balloon angioplasty, cerebral infarction, cerebral hemorrhage, or any leg operation
MORGAM-FIN MORGAM-FRA MORGAM-GER MORGAM-ITA MORGAM-	MONICA, Risk, Genetics, Archiving, and Monograph	15561751 ref1	European	Finland: Southern Finland, North Karelia, Kuopio Province, Oulu Province, Turku/Loimaa, Helsinki. France: Lille, Strasbourg, Toulouse. Germany: Augsburg. Italy: Brianza. United Kingdom:	CAD/MI	All CAD: Incident definite or possible MI or coronary death, or unstable angina during follow-up, Coronary revascularization during follow-up, Documented MI at baseline, or an unclassifiable coronary death during follow-up. MI:Definite myocardial infarction.	Controls are 1:1 matched for cases (by age, sex, and region). They are participants who remained free of any cardiovascular disease at the age when the matched case had the first event.

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UNK				Belfast.			
OHGS	The Ottawa Heart Genomics Study	17478681	European	Canada	CAD/MI	Cases had at least one of myocardial infarction, coronary artery bypass graft, percutenaeous intervention or a stenosis of at least 50% in at least one epicardial vessel. Diabetic cases and cases aged greater than 55 for men or 65 for women were excluded.	Controls were either asymptomatic for cardiovasular disease or had had a CTA or angiogram demonstrating no stenosis of greater than 50%. Controls were required to be at least 65 years old for men and 70 years old for women at the time of recruitment.
PIVUS	Prospective Investigation of the Vasculature in Uppsala Seniors	18489581	European	Sweden	CAD	Individuals within this cohort study who developed a fatal or non-fatal myocardial infarction or unstable angina during follow-up. Participants were identified as having CHD if they had a hospital admission with CHD as the primary cause of hospitalization and/or died with CAD as the underlying cause. CHD was defined as acute myocardial infarction (ICD-8 and ICD-9 code 410, ICD-10 codes I21-I22) or unstable angina (ICD-8 code 411, ICD-9 code 411B, ICD-10 code I20.0). The positive predictive values (i.e. validity) of the CHD diagnosis in the Swedish hospital discharge register has been demonstrated to be at least 95% when only primary diagnoses are considered.	Non-cases from the same longitudinal, community-based cohort study
PMB	Pfizer-MGH-Broad		European	Finland, Sweden	CAD/MI		
PopGen	PopGen	18362232	European	Germany	CAD	Unrelated German CAD patients recruited in Schleswig-Holstein, through the population-based PopGen biobank with significant CAD (at least a 70% stenosis in one major coronary vessel); age of onset < 55 y	population based controls
PROCARDIS	European collaborative study of the genetics of precocious coronary artery disease	18048406	European	Germany, Italy, Sweden, UK	CAD/MI	Symptomatic CAD before age 66 years and 80% of cases also had a sibling in whom CAD had been diagnosed before age 66 years. CAD was defined as clinically documented evidence of myocardial infarction (MI) (80%),	PROCARDIS controls had no personal or sibling history of CAD before age 66 years. PoBI and UK Twin study are population-based controls that were not screened for CAD.

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						coronary artery bypass graft (CABG) (10%), acute coronary syndrome (ACS) (6%), coronary angioplasty (CA) (1%) or stable angina (hospitalization for angina or documented obstructive coronary disease) (3%). The cases included 2,136 cases who were half or full siblings.	
PROMIS*	The Pakistan Risk Of Myocardial Infarction Study	19404752	South Asian	Pakistan	CAD/MI	Acute myocardial infarction (MI) with typical ECG characteristics, a positive troponin test, and MI symptoms within the previous 24 hours	Controls have been recruited in the following order of priority: (i) visitors of patients attending the out-patient department; (ii) patients attending the out-patient department for routine non-cardiac complaints, or (iii) non-blood related visitors of index MI cases.
SCARF-SHEEP			European	Sweden	CAD/MI	First confirmed myocardial infarction	No history, symptoms or signs of cardiovascular disease
STR	Swedish Twin Registry	8981957	European	Sweden	CAD	Individuals within this cohort study who developed a fatal or non-fatal myocardial infarction or unstable angina during follow-up. Participants were identified as having CHD if they had a hospital admission with CHD as the primary cause of hospitalization and/or died with CAD as the underlying cause. CHD was defined as acute myocardial infarction (ICD-8 and ICD-9 code 410, ICD-10 codes I21-I22) or unstable angina (ICD-8 code 411, ICD-9 code 411B, ICD-10 code I20.0). The positive predictive values (i.e. validity) of the CHD diagnosis in the Swedish hospital discharge register has been demonstrated to be at least 95% when only primary diagnoses are considered.	Non-cases from the same longitudinal, community-based cohort study
THISEAS	The Hellenic Study of Interactions between Snps and Eating in Atherosclerosis Susceptibility	20167083	European	Greece	CAD/MI	First-ever mi before age of 70 yrs; first CAD (>50% stenosis in one of the three main coronary vessels assessed by coronary artery angiography - no history of ACS)	<30% stenosis assessed by coronary artery angiography or negative stress test; age matched without MI/CAD history

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	(THISEAS) study						
ULSAM	Uppsala Longitudinal Study of Adult Men	12637978	European	Sweden	CAD/MI	Individuals within this cohort study who developed a fatal or non-fatal myocardial infarction or unstable angina during follow-up. Participants were identified as having CHD if they had a hospital admission with CHD as the primary cause of hospitalization and/or died with CAD as the underlying cause. CHD was defined as acute myocardial infarction (ICD-8 and ICD-9 code 410, ICD-10 codes I21-I22) or unstable angina (ICD-8 code 411, ICD-9 code 411B, ICD-10 code I20.0). The positive predictive values (i.e. validity) of the CHD diagnosis in the Swedish hospital discharge register has been demonstrated to be at least 95% when only primary diagnoses are considered.	Non-cases from the same longitudinal, community-based cohort study
WTCCC CAD2	The Wellcome Trust Case Control Consortium CAD2		European	UK	CAD/MI		1958 Birth Cohort

* submitted datasets with independent samples either directly genotyped on the Metabochip or results from GWAS

ref1 Tunstall-Pedoe H, editor. Prepared by Tunstall-Pedoe H, Kuulasmaa K, Tolonen H, Davidson M, Mendis S with 64 other contributors for The WHO MONICA Project. MONICA Monograph and Multimedia Sourcebook. Geneva: World Health Organization; 2003. ISBN 92 4 156223 4. Also available from http://www.ktl.fi/monica/public/monograph.html.

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Supplementary Table 2b: General Study Characteristics for Stage 3 studies

Study	Full Study name	Reference	Ethnicity	Region of recruitment	Phenotype	Phenotype definition	Control definition
COROGENE	Corogene	21642350	European	Helsinki, Finland	Acute coronary syndrome patients	Acute coronary syndrome cases with coronary artery obstruction >50% at least in one coronary artery.	Area matched, healthy FINRISK population controls
FINCAVAS	The Finnish Cardiovascular Study	16515696	European	Finland	CAD/MI	Cases defined as >50% stenosis in one or more coronary arteries in coronary angiography, or strong Bayesian posterior probability for CAD after exercise test using a bicycle ergometer, or hospital verified myocardial infarction in history. Patients were recruited during 2001-2007, and the follow-up data was gathered at 2, 5 and 10 years.	Controls defined as <50% stenosis in coronary arteries, or low Bayesian posterior probability for CAD after exercise test, and no myocardial infarction in medical history.
GenRIC	Genomics Research in Cardiovascular disease	NA	East Asian	Seoul, Korea	CAD/MI	Angiographic definition: Significant reduction in luminal diameter due to coronary atheromatous disease (i.e. with stenosis greater than 50%) Clinical definitions: Stable angina: chest or arm discomfort that may not be described as pain but is reproducibly associated with physical exertion or stress and is relieved within 5-10 minutes by rest and/or sublingual nitroglycerin. Unstable angina: Angina pectoris or equivalent ischemic discomfort with at least one of three features 1) it occurs at rest, usually resting > 10 minutes, 2) it is severe and of new onset (≤4-6 weeks), 3) it occurs with a crescendo pattern Myocardial infarction: Spontaneous or secondary myocardial infarction according to the "universal definition of myocardial infarction"	Participants without CAD from a population based cohort

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Supplementary Table 3a: Genotyping, Quality control and Statistical analysis for Stage 2 studies

Study	Genotyping Array	Genotyping Centre	Calling algorithm	Ethnicity	PCA/Additional QC	Imputation software/ Reference panel	Total SNPs submitted in ALL analysis [genotyped/imputed]	SNPs passing QC[1]	Analysis software	λ_{QT}
ADVANCE	Illumina CM[2]	HudsonAlpha	GenCall	European	Ethnic outliers, gender mismatch,	NA	193881/0	134,901	Plink	1.00
AMC-PAS	Illumina CM[2]	Sanger	GenoSNP	European	Heterozygosity, ethnic outliers, duplicates	NA	117088/0	117,088	Plink	1.08
Angio-Lueb/ KORA F3	Illumina CM[2]	Helmholtz Zentrum München	GenCall	European	Gender check, MDS adjustment, IBS/IBD check	NA	130610/0	130,609	Plink	1.08
Cardiogenics	Illumina CM[2]	Sanger	GenoSNP	European	Heterozygosity, ethnic outliers, duplicates Center site study specific adjustment	NA	122839/0	122,839	Plink	1.07
DILGOM	Illumina CM[2]	Helsinki	Illuminus	European	NA	NA	181174/0	121,295	Plink	1.00
DUKE	Affymetrix Axiom	Canadian Cardiovascular Genetics Centre	BRLMM-P	European	Ethnic outliers, duplicates SNP call rate ≥ 95%, MAF ≥ 5%, HWE P > 10^{-6}	IMPUTE v2.1.0 1kG first generation CEU + TSI	22455/74180	84,212	R	1.01
EGCUT GWAS	Illumina Human370CNV & OmniExpress	Estonian Genome Center of University of Tartu	Beadstudio	European	Ethnic outliers, gender check, cryptic relatedness PCA SNP call rate ≥ 95%, HWE P > 10^{-6}	IMPUTE v1.0 CEU build36 rel22	178087/2239235	85,852	SNPTEST	1.10
EGCUT Metabochip	Illumina CM[2]	Estonian Genome Center of University of Tartu	Beadstudio	European	Ethnic outliers, gender check, cryptic relatedness	NA	181174/0	128,757	Plink	1.06
EPIC	Illumina CM[2]	Sanger	GenoSNP	European	Heterozygosity, ethnic outliers	NA	122022/0	122,022	Plink	1.11
FGENTCARD	Illumina Human610-Quad, Human 660W-Quad	CNG, IntegraGen	GenCall	European	Phenotyping, ethnicity, heterozygosity, Beadchip PC SNP call rate ≥ 98%, HWE P > 10^{-7}	Impute2 Hapmap2 rel22 CEU	513079/2100829	94,198	R/SNPTEST2	1.02
FRISCII GLACIER	Illumina CM[2]	Uppsala SNP&SEQ Technology Platform / Sanger	GenTrain 2.0 Illuminus	European	Heterozygosity, ethnic outliers, duplicates, missingness, HWE, gender mismatch, PCA FRISCII SNP call rate ≥ 98%, HWE P > 10^{-6} GLACIER SNP call rate ≥ 95%	NA	178783/0 150451/0	128,200	GenABEL	1.24
GoDARTS	Illumina CM[2]	Sanger	GenoSNP	European	Heterozygosity, ethnic outliers, duplicates, SNP call rate ≥ 98%,, MAF>0.01	NA	107402/0	118,658	SNPTEST	1.03
HPS	Illumina 610-Quad (cases and UK Twins controls) Illumina 1M Duo (WTCCC2 NBS controls,	CNG, Evry, France	Beadstudio and Illuminus	European	Non-European ancestry, duplicates SNP call rate ≥97.5%, HWE P > 10^{-6}	MACH HapMap2 rel22	95610	92,881	Plink	1.05

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	subset of 610k SNPs used for imputation)									
ITH	Affymetrix 6.0	Canadian Cardiovascular Genetics Centre	Birdseed - v2	European	Ethnic outliers, duplicates SNP call rate ≥ 95%, HWE P > 10^{-6}	IMPUTE v2.1.0 1kG first generation CEU + TSI	27073/69976	86,750	R	1.00
LOLIPOP	Illumina Human610	DeCode	Beadstudio	South Asian	Ethnic outliers, duplicates, wrong gender, relatedness Principal components, cohort SNP call rate ≥95%, HWE P > 10^{-6} MAF ≥ 1%	MACH HapMap2 rel 21 combined data	544390/1710717	82,193	Plink/ MACH2qtl	1.05
LURIC-EMIL	Illumina CM[2]			European	Heterozygosity, ethnic outliers Principal components	NA	128596/0	128,596	Plink	1.13
METSIM	Illumina CM[2]	CIDR	Beadstudio	European	Dropped SNP if Cluster Separation score < 0.2 (based on re-clustering using all samples) or which had more than 1 Replicate error as defined with the HapMap control samples. Hand editing for X, Y and Mitochondrial loci. Call rate >= .95, based on genotypes with quality score threshold 0.15. Duplicate and gender check	NA	138992/0	129,131	Plink	1.02
MORGAM-FIN	Illumina CM[2]	Sanger	GenCall	European	Heterozygosity, ethnic outliers, duplicates, gender check, relatedness SNP call rate ≥ 99%	NA	128920/0	123,461	Plink	1.00
MORGAM-FRA	Illumina CM[2]	Sanger	GenCall	European	Heterozygosity, ethnic outliers, duplicates, gender check, relatedness SNP call rate ≥ 99%	NA	127793/0	120,156	Plink	1.04
MORGAM-GER	Illumina CM[2]	Sanger	GenCall	European	Heterozygosity, ethnic outliers, duplicates, gender check, relatedness SNP call rate ≥ 99%	NA	125969/0	120,099	Plink	0.90
MORGAM-ITA	Illumina CM[2]	Sanger	GenCall	European	Heterozygosity, ethnic outliers, duplicates, gender check, relatedness SNP call rate ≥ 99%	NA	129634/0	121,514	Plink	1.01
MORGAM-UNK	Illumina CM[2]	Sanger	GenCall	European	Heterozygosity, ethnic outliers, duplicates, gender check, relatedness SNP call rate ≥ 99%	NA	124600/0	120,268	Plink	1.04
OHGS	Affymetrix 500K and 6.0	Canadian Cardiovascular Genetics Centre	BRLMM and Birdseed-v2	European	Ethnic outliers, duplicates SNP call rate ≥ 95%, HWE P > 10^{-6}	IMPUTE v2.1.0 1kG first generation CEU + TSI	26907/ 69887	86,151	R	1.16
PIVUS	Illumina CM[2]	Uppsala SNP&SEQ Technology Platform	GenCall	European	SNP call rate ≥ 90%, HWE P > 10^{-6}	NA	133388/0	126,040	Plink	0.95
PMB	Illumina CM[2]	Broad Institute	Birdseed	European	batch excluded based on heterozygosity, missingness	NA	179195/0	121,812	Plink	1.01

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					outliers					
PopGEN	Illumina CM[2]	Helmholtz Zentrum München	GenCall	European	Gender check, IBS/IBD check	NA	125243/0	125,243	Plink	1.04
PROCARDIS	Illumina Infinium Human 1M, HumanHap 610 and Human 1.2M (WTCCC2 bespoke)	CNG, Evry, France and Sanger, UK	Beadstudio and Illuminus	European	Non-European ancestry outliers, duplicates Country of origin robust(Huber-White/sandwich) standard error estimates to allow for relatedness SNP call rate ≥ 97.5%, HWE P > 10^{-6}	MACH HapMap2 r22	29957/65653	94,381	STATA	1.06
PROMIS GWAS	Illumina Quad 660	Sanger	GenoSNP	South Asian	Heterozygosity, ethnic outliers, duplicates, PCA SNP call rate ≥97.5%, HWE P > 10^{-6}	Impute v2 Hapmap2 + Hapmap 3 GIH	529030/2670976	97,920	SNPTESTv2	1.05
PROMIS Metabochip	Illumina CM[2]	Sanger	GenoSNP	South Asian	Heterozygosity, ethnic outliers, duplicates	NA	127574/0	127,574	Plink	1.05
SCARF-SHEEP	Illumina CM[2]	Uppsala, Sweden	GenCall	European		NA	180475/0	125,894	Plink	1.07
STR	Illumina CM[2]	Uppsala SNP&SEQ Technology Platform	GenCall	European	SNP call rate >90%, HWE p>10^{-6}	NA	133430/0	127,479	Plink	1.03
THISEAS	Illumina CM[2]	Sanger	GenoSNP	European	Heterozygosity, ethnic outliers, gender mismatch	NA	121533/0	121,533	Plink	0.95
ULSAM	Illumina CM[2]	Uppsala SNP&SEQ Technology Platform	GenCall	European	SNP call rate >90%, HWE p>10^{-6}	NA	129336/0	123,677	Plink	1.10
WTCCC CAD2	Illumina CM[2]	Sanger	GenoSNP	European	Duplicates	NA	171730/0	120,383	Plink	0.89

MAF = Minor allele frequency, OR = Odds Ratio, HWE = Hardy Weinberg E…

[1]QC was applied to all studies centrally, Sample Call Rate > 0.98, MAF (in Cases and Controls) ≥ 0.001, HWE (Controls) ≥ 0.0001

[2] Illumina Cardio-Metabochip

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Supplementary Table 3b: Genotyping, quality control and Statistical analysis for Stage 3 studies

Study	Genotyping Array	Genotyping Centre	Calling algorithm	Ethnicity	PCA/Additional QC	Imputation software/ Reference panel	Total SNPs submitted in ALL analysis [genotyped/imputed]	SNPs passing QC[1]	Analysis software	λ_{QT}
COROGENE	Illumina 610K	Sanger	Illuminus	European	heterozygosity, gender check and relatedness checks have been performed and any discrebansies have been removed. 8 individuals have been removed due to cryptic relatedness.	MACH, Hapmap 2	5/54 (replication snps)	59	Probabel	
FINCAVAS	Illumina CM[2]	Helmholtz Zentrum München	GenCall	European	Heterozygosity, relatedness, gender mismatch	NA	161183/0	123522	SNPTEST v2.2.0	0.99
GenRIC	Affymetrix Human SNP array 6.0	Korea National Institute of Health	BirdSeed	East Asian	Gender, Heterozygosity, cryptic first degree relatives	IMPUTE (Ver1.0)	599,226/ 1,631,947	52724	R package	1.12

MAF = Minor allele frequency, OR = Odds Ratio, HWE = Hardy Weinberg E…

[1]QC was applied to all studies centrally, Sample Call Rate > 0.98, MAF (in Cases and Controls) ≥ 0.001, HWE (Controls) ≥ 0.0001

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Supplementary Table 4: Loci not reaching genome-wide significance in Stage 3

SNP	Chr	Nearest Gene(s)	Effect/Non Effect allele (frequency)	Stage 1		Stage 2		Combined (Stage 1,2)	Stage 3		Combined (Stage 1,2,3)
				OR	*P*	OR	*P*	*P*	OR	*P*	*P*
rs246600	5	ARHGAP26/KIAA0621	C/T (0.46)	1.06	1.16E-04	1.04	7.55E-05	1.71E-07	1.01	8.05E-01	2.36E-07
rs11057841	12	SCARB1	T/C (0.15)	1.11	7.22E-05	1.06	1.10E-04	1.56E-07	1.02	7.45E-01	1.78E-07
rs7219320	17	TOM1L2/LRRC48/ATPAF2	A/G (0.40)	1.07	1.37E-05	1.04	6.62E-04	1.77E-07	1.01	7.23E-01	4.95E-07
rs867186	20	PROCR	A/G (0.88)	1.08	1.56E-03	1.07	1.23E-05	3.59E-07	1.08	1.51E-01	5.12E-08

The combination of Stage 1, 2and 3 was performed using a sample size weighted meta-analysis.

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Supplementary Table 5: Subgroup analyses results

			Males		Females		Young		Old		MI	
Known Loci	**SNP**	**Effect/ Non Effect allele**	**Stage 2 OR**	**Stage 1 and Stage 2 *P***	**Stage 2 OR**	**Stage 1 and Stage 2 *P***	**Stage 2 OR**	**Stage 1 and Stage 2 *P***	**Stage 2 OR**	**Stage 1 and Stage 2 *P***	**Stage 2 OR**	**Stage 1 and Stage 2 *P***
SORT1	rs602633	G/T	1.14	1.32E-18	1.06	3.42E-05	1.21	2.77E-20	1.10	4.97E-08	1.11	2.23E-16
PCSK9	rs11206510	T/C	1.05	1.55E-02[1]	1.02	4.07E-01[1]	1.07	2.04E-02[1]	1.04	7.12E-04[1]	1.05	7.03E-05
WDR12	rs6725887	C/T	1.09	1.88E-07	1.11	6.55E-08	1.04	1.70E-04	1.10	1.48E-07	1.09	5.51E-10
MRAS	rs9818870	T/C	1.07	2.97E-07	1.01	1.84E-02	1.03	1.06E-05	1.05	3.26E-07	1.06	6.44E-11
TCF21	rs12190287	C/G	1.06	3.51E-09	1.04	7.54E-03	1.04	7.78E-04	1.05	5.34E-09	1.05	3.05E-10
SLC22A3/LPAL2/LPA	rs3798220	C/T	1.25	3.62E-03[1]	1.39	2.14E-03[1]	n/a	n/a	1.22	2.13E-03[1]	1.26	2.09E-03[1]
	rs2048327	C/T	1.05	9.55E-07	1.05	3.75E-05	1.06	1.51E-07	1.05	8.31E-08	1.04	2.59E-06
ZC3HC1	rs11556924	C/T	1.08	4.83E-12	1.08	4.70E-05	1.08	5.73E-10	1.06	4.68E-07	1.07	3.18E-12
CDKN2BAS	rs1333049	C/G	1.23	3.93E-88	1.17	4.42E-24	1.23	3.01E-61	1.20	4.03E-41	1.21	2.57E-80
	rs3217992	T/ C	1.16	4.66E-48	1.09	1.57E-08	1.15	5.43E-31	1.14	6.01E-36	1.14	5.69E-41
ABO	rs579459	C/T	1.04	2.82E-08	1.04	2.20E-03	1.04	1.22E-04	1.03	2.15E-04	1.03	2.17E-07
CYP17A1/CNNM2/NT5C 2	rs12413409	G/A	1.07	1.11E-05	1.11	2.20E-06	1.06	1.67E-06	1.08	1.36E-07	1.09	5.33E-08
KIAA1462	rs2505083	C/T	1.06	4.16E-08	1.04	3.36E-03	1.07	5.74E-06	1.05	1.91E-06	1.05	2.14E-04
PDGFD	rs974819	T/C	1.09	5.41E-10	1.04	1.43E-02	1.13	3.44E-09	1.07	1.89E-08	1.07	6.99E-09
SH2B3	rs3184504	T/C	1.06	3.23E-06	1.08	8.11E-05	n/a	n/a	1.07	1.58E-10	n/a	n/a
COL4A1/COL4A2	rs4773144	G/A	1.07	2.76E-09	1.03	7.37E-03	1.05	2.54E-05	1.06	1.32E-07	1.05	7.08E-07
	rs9515203	T/C	1.08	5.39E-09	1.04	6.98E-03	1.10	3.08E-09	1.06	3.90E-04	1.05	1.40E-06
HHIPL1	rs2895811	C/T	1.04	1.35E-03[1]	1.03	1.03E-01[1]	1.05	2.10E-02[1]	1.04	3.04E-03[1]	1.04	7.47E-03[1]
RAI1/PEMT/RASD1	rs12936587	G/A	1.04	5.97E-08	1.04	1.06E-02	1.05	1.34E-05	1.03	2.27E-06	1.04	5.50E-08
LDLR	rs1122608	G/T	1.07	4.52E-10	1.05	2.87E-02	1.07	2.70E-09	1.06	7.00E-07	1.06	5.39E-08
gene_desert/KCNE2	rs9982601	T/C	1.09	3.81E-09	1.09	1.72E-03	1.13	1.90E-12	1.09	7.18E-08	1.07	1.74E-10
PPAP2B	rs17114036	A/G	1.08	8.07E-08	1.10	2.66E-04	1.08	8.23E-04	1.10	1.43E-09	1.09	2.16E-08
ANKS1A	rs12205331	C/ T	1.02	1.43E-04	1.01	4.95E-02	0.99	1.69E-03	1.02	5.73E-03	1.02	6.44E-04
PHACTR1	rs9369640	A/ C	1.10	2.96E-18	1.05	2.29E-06	1.10	1.17E-08	1.09	1.49E-10	1.10	8.55E-20
CXCL12	rs501120	T/ C	1.06	1.25E-05	1.06	1.39E-04	1.09	6.49E-08	1.04	3.18E-07	1.08	8.56E-11
	rs2047009	G/ T	1.06	9.41E-11	1.02	9.89E-02	1.07	3.50E-08	1.04	3.43E-06	1.04	8.24E-07
LIPA	rs2246833	T/ C	1.06	2.39E-06	1.02	2.25E-01	1.08	6.86E-07	1.03	2.46E-04	1.05	2.29E-08
	rs11203042	T/ C	1.03	4.23E-04	1.02	5.19E-02	1.04	3.86E-06	1.02	8.25E-05	1.02	3.09E-07
UBE2Z	rs15563	G/A	1.01	5.82E-05	1.02	6.39E-03	1.01	3.86E-04	1.01	2.93E-03	1.01	1.68E-03
SMG6	rs2281727	G/A	1.04	1.33E-05	1.01	4.98E-03	1.05	2.94E-10	1.03	6.46E-05	1.04	2.63E-07
MIA3	rs17464857	T/ G	1.03	9.80E-03	1.01	5.88E-02	1.02	2.61E-02	1.04	1.14E-03	1.03	8.77E-04
ZNF259/APOA5/APOA1	rs9326246	C/G	1.03	1.92E-04	1.09	1.03E-03	1.02	1.16E-01	1.05	2.27E-04	1.04	1.69E-04
ADAMTS7	rs7173743	T/C	1.05	2.78E-08	1.06	2.23E-05	1.06	1.96E-06	1.06	1.92E-09	1.06	1.57E-10
ApoE/ApoC1	rs2075650	G/A	1.11	6.72E-08[1]	1.12	1.08E-04[1]	1.17	4.56E-08[1]	1.09	7.10E-07[1]	1.12	6.54E-09[1]
	rs445925	G/A	1.14	2.01E-07[1]	1.10	9.52E-03[1]	1.15	1.99E-04[1]	1.11	3.26E-03[1]	1.13	2.50E-07[1]
Novel loci												
IL6R	rs4845625	T/C	1.03	6.55E-05	1.07	3.74E-04	1.05	2.01E-04	1.04	3.67E-05	1.05	4.30E-07
APOB	rs515135	C/T	1.08	2.93E-09	1.07	2.47E-02	1.07	2.57E-04	1.08	5.42E-08	1.08	1.96E-09
ZEB2-AC074093.1	rs2252641	C/T	1.04	4.19E-06	1.05	9.80E-04	1.04	9.88E-04	1.04	6.44E-05	1.03	5.03E-04
GGCX/VAMP8	rs1561198	T/C	1.06	1.66E-07	1.02	1.00E-01	1.08	1.43E-09	1.04	1.60E-03	1.06	1.77E-07
GUCY1A3	rs7692387	G/A	1.05	1.12E-06	1.06	2.55E-03	1.03	1.34E-02	1.06	4.06E-06	1.04	8.87E-05

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SLC22A4/SLC22A5	rs273909	G/A	1.09	9.14E-07	1.09	9.16E-03	1.08	1.34E-03	1.08	5.58E-05	1.07	9.68E-04
KCNK5	rs10947789	T/C	1.07	6.86E-06	1.02	9.64E-02	1.08	2.05E-04	1.05	1.14E-04	1.07	3.65E-08
PLG	rs4252120	T/C	1.04	7.93E-06	1.10	1.48E-05	1.07	7.44E-05	1.06	3.54E-05	1.06	1.56E-05
LPL	rs264[2]	G/A	1.06	5.39E-07	1.05	1.88E-03	1.06	6.04E-06	1.07	3.45E-07	1.04	7.38E-08
	rs894210[2]	G/A	1.04	1.41E-06	1.02	6.45E-02	1.03	6.17E-04	1.04	1.47E-07	1.04	2.99E-06
	rs1569209[2]	T/G	1.12	8.30E-07	1.03	5.65E-02	1.11	1.67E-07	1.13	2.41E-07	1.08	1.19E-06
FLT1	rs9319428	A/G	1.05	1.79E-07	1.06	5.41E-03	1.06	4.49E-04	1.05	6.74E-07	1.05	4.16E-05
FURIN/FES	rs17514846[3]	A/C	1.05	2.06E-07	1.06	6.47E-04	1.03	3.21E-03	1.06	1.27E-08	1.07	1.52E-09
	rs4932370[3]	A/G	1.06	1.03E-07	1.07	5.51E-04	1.05	1.60E-02	1.07	8.44E-08	1.06	2.81E-05
TRIB1	rs2954029	A/T	1.05	4.22E-06	1.02	2.45E-04	1.06	5.49E-07	1.05	6.26E-05	1.04	1.03E-05
ABCG5/ABCG8	rs6544713	T/C	1.07	1.21E-10	1.06	4.60E-03	1.07	1.55E-04	1.05	1.53E-06	1.05	4.43E-05
EDNRA	rs1878406	T/C	1.06	6.23E-08	1.06	1.37E-03	1.07	1.43E-04	1.07	5.32E-06	1.05	3.96E-03
HDAC9	rs2023938	C/T	1.07	2.30E-05	1.11	1.39E-03	1.07	3.02E-03	1.07	1.71E-04	1.09	1.24E-03
AK097927	rs16986953	A/G	1.11	2.00E-08	1.03	5.06E-01	1.17	1.68E-08	1.11	5.52E-04	1.10	4.06E-06

Males: Logistic regression of all male cases versus all male controls, adjusted for age; Females: Logistic regression of all female cases versus all female controls, adjusted for age; Young: Logistic regression of all cases with early age of onset (<=50 years) versus all controls, adjusted for sex; Old: Logistic regression of all cases with late age of onset (>50 years) versus all controls, adjusted for sex; MI: Logistic regression of all MI cases versus all controls, adjusted for age and sex

[1]Stage 2 p-value
[2]Pair-wise R^2: rs264-rs894210 0.13; rs264-rs1569209 0.43; rs894210-rs1569209 0.12
[3] Pair-wise R^2: rs17514846-rs4932370 0.41

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Supplementary Table 6: Expression Analyses

Locus	SNP ID	CAD SNP	r^2 with lead SNP (CEU)	Transcript	Tissue	*p*-value	Strongest eQTLassociation: *cis*-eSNP	r^2 with lead SNP (CEU)	*p*-value	*Conditional p*-value
cis- Expression QTL Analysis										
VAMP5-VAMP8-GGCX	rs1561198	Lead		*VAMP8*	LCL	1.13E-19	rs3770098	0.87	3.50E-23	0.95
	rs1561198	Lead		*VAMP8*	Skin	1.38E-13	rs6757263	0.90	2.48E-17	0.0778
	rs1561198	Lead		*GGCX*	mammary artery		rs12714147	0.18	3.92E-05	0.273
	rs1561198	Lead		*GGCX*	Liver	0.00053	rs11680227	0.30	0.000637	0.058
	rs1561198	Lead		*GGCX*	subqutaneous fat	9.88E-16	rs6705971	0.94	5.94E-23	0.473
	rs1561198	Lead		*GGCX*	omentum	1.97E-07	rs6738645	0.94	2.45E-12	0.172
PLG	rs4252120	Lead		*PLG*	LCL	1.29E-14	rs4252165	0.96	9.85E-16	0.09
FURIN- FES	rs17514846	Lead	0.611*	*FES*	LCL	5.74E-23	rs6227	0.46	4.50E-33	0.013
	rs4932178	proxy		*FES*	Fibroblasts	3.4E-04	rs4932178	1	n/a	n/a
	rs17514846	Lead		*FES*	omentum	1.9E-04	rs17514846	1	n/a	n/a
	rs17514846	Lead		*FURIN*	omentum	4.81E-13	rs4702	0.57	3.92E-30	1.1E-04
	rs17514846	Lead		*FES*	subqutaneous fat	1.10E-08	rs17514846	1	n/a	n/a
	rs17514846	Lead		*FURIN*	subqutaneous fat	7.44E-08	rs6227	0.46	9.41E-21	0.0034
Allelic Imbalance Expression Analysis										
VAMP5-VAMP8-GGCX	rs1561198	Lead		*GGCX*	LCL (HapMap CEU)	1.35E-08	rs6739015	0.87	4.64E-11	
	rs1561198	Lead		*GGCX*	Fibroblasts	8.37E-10	rs7591175	0.87	1.29E-10	
	rs1561198	Lead		*GGCX*	monocytes	1.43E-25	rs699664	0.667	1.57E-31	2.48E-05
LPL	rs264	Lead		*LPL*	monocytes	1.72E-13	rs269	0.725	1.23E-15	
FURIN- FES	rs4932179	proxy	0.656	*FES*	monocytes	7.00E-14	rs4932179	1	n/a	
	rs2071410	proxy	0.86*	*FES*	LCL (HapMap CEU)	1.23E-05	rs1573643	0.8	1.08E-05	

* r^2 to rs2521501 which is independent signal to rs17514846

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Supplementary Table 7a: Mouse Model Details for Novel Loci

					If Cardiovascular or Metabolic genotype		
SNP	Chr	Nearest Gene(s)	Homozygous null Phenotype	Affected Anatomical Systems	Strain/Stock Designation	Reference (PubMed)	Affected systems
rs4845625	1	IL6R	Defective T helper 17 cell development. Abnormal inflammatory response and abnormal wound healing.	Ho, Im, A, L, En	NA		
rs6544713	2	ABCG5	Hyperabsorption of dietary plant sterols. Sitosterolemia, anemia, leukopenia, macrothrombocytopenia, other hematologic defects, cardiomyopathy, high plasma phytosterol levels and premature death.	C, Ho, L, Mo, Rp, He, B, G, Im, Mu	Abcg5^{trac}	19846887	Cardiac fibrosis, Cardiomyopathy
					Abcg5/Abcg8^{tm1Hobb}	12444248	Abnormal intestinal lipid absorption abnormal circulating lipid level, decreased cholesterol abnormal cholesterol homeostasis
		ABCG8	Fail to secrete cholesterol into bile and exhibit increased plasma and tissue plant sterol levels	D, Ho, L, He	Abcg8^{tm1Elk}	15040800	Increased circulating plant sterol and triglyceride, decreased circulating cholesterol
rs515135	2	APOB	Usually die by midgestation; longer survivors exhibit exencephaly. Heterozygotes show reduced plasma cholesterol and apolipoprotein levels.	C, Em, G, Ho, L, Mo, N	Apob^{tm4Sgy} *Apob^{tm2Sgy}* Apob$^{tm1.1Zc}$ Apob^{tm1Mae}	9502790 8692825 10893242	Hemorrhage Atherosclerotic lesions decreased circulating triglyceride, HDL, LDL, VLDL
rs2252641	2	ZEB2	No Mouse model Variety of defects at embryonic day 8.5 and die between E9.5 and 10.5.	NA Mo, Ey, Rp, G, N, Em	NA NA		
		ACVR2A	Most appear normal, a few display skeletal and facial abnormalities. As adults, follicle-stimulating hormone is suppressed, affecting reproduction.	C, Mo, G, Ey, Rp, N, Em, En, S	Acvr2a^{tm1Hsch}	10452853	Transposition of great arteries Abnormal heart development
rs1561198	2	GGCX	50% of embryos die between E9.5 and E18, those surviving to term die of massive intra-abdominal hemorrhage shortly after birth with no evidence of ectopic calcification	C, Ho, Mo, S	Ggcx^{tm1Dgi}	17327402	Internal hemorrhage
		VAMP8	Postnatal lethality, hydronephrosis, and reduced amylase secretion, type I hypesensitivity reaction, and platelet activation	Ho, Rn, B, Mo, En, Im, D, G, He	NA		
rs7692387	4	GUCY1A3	Mild elevation of systolic blood pressure, abnormal blood vessel and platelet responses to NO	C, Rs, Mo, He, Ho, Mu	Gucy1a3$^{tm1.1Brou}$ Gucy1a3$^{tm1.1Dko}$	16886062 16614755	Abnormal right ventricle pressure

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							Increased systemic arterial blood pressure Abnormal vasodilation Abnormal platelet aggregation
rs1878406	4	EDNRA	Perinatal death with cardiac and craniofacial malformations	C, Ho, Mo, N, R, Mu, En, Em, D, I, Rs, S, He	Ednra$^{tm2.1Hku}$ Ednra^{tm5Hku} Ednra^{tm1Ywa}	18199583 20929948 9449664	Abnormal heart morphology
rs273909	5	SLC22A4 SLC22A5	No Mouse model Systemic carnitine deficiency, cardiac hypertrophy, impaired Na-dependent carnitine transport, fatty liver, hypoglycemia, high postnatal mortality, and male infertility	NA C, Mo, G, Ho, L, Rn, Rp	NA Slc22a5^{jvs}	 Mouse Genome 86,Hayakawa *et al*	 Cardiac hypertrophy abnormal glucse homeostasis/ hypoglycemia
rs10947789	6	KCNK5	Smaller than normal and prenatal lethality depending on genetic background.	Rs, N, Mo, G, Rn	NA		
rs4252120	6	PLG	Retarded growth, variable rectal prolapse, impaired fertility and lactation in females, early mortality, and widespread fibrin deposition and thrombotic lesions in liver, lung, stomach and other tissues.	C, D, En, G, Ho, Im, Int, L, Mo, N, Rn, Rp, Rs, T, Ey	Plg^{tm1Jld}	7705657	Decreased angiogenesis Venoocclusion Atherosclerotic lesions Abnormal heart morphology Abnormal blood coagulation and wound healing Decreased circulating HDL
rs2023938	7	HDAC9	Mice with disruptions in this gene display age dependent cardiac hypertrophy	C, Mo, G, Mu	Hdac9^{tm1Eno}	12202037	Cardiac hypertrophy Ventricular septal defect hemorrhage abnormal myocardium layer morphology
rs264	8	LPL	Cyanotic and die within 2 days of birth due to chylomicron engorgement of capillaries. Mutants show hypertriglyceridemia and reduced fat stores..	C, Ho, Mu, Mo	Lpl^{tm1Ijg} Lpl^{tm1Sem} Lpl^{tm1Bres}	15028738 7759497 8675619	Cardiac fibrosis Abnormal cardiovascular system physiology Decreased cardiac muscle contractility Increased left ventricle diastolic and systolic pressure Decreased circulating HDL, LDL Increased circulating VLDL and triglyceride level Abnormal glucose homeostasis Thrombosis
rs2954029	8	TRIB1	Macrophages exhibit impaired IL12 response to LPS, MALP-1, or CpG DNA.	G, Im	NA		
rs9319428	13	FLT1	exhibit an excess of hemangioblasts resulting in an overgrowth of endothelial cells, abnormalities of vascular	C, Ey, Em, He, Mo, Ho, Mu, G	Flt1^{tm1Jrt}	7596436	Abnormal heart development and blood vessel morphology

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			channels and blood islands,				Increased angiogenesis Abnormal blood circulation Increased response of heart to induced stress
rs17514846	15	FURIN	Die at E10.5-E11.5. multiple tissue abnormalities including abnormal yolk sac vasculature and chorioallantoic fusion, failure of axial rotation, a kinked neural tube, exencephaly and severe ventral closure and cardiac defects.	C, Mo, Em, G, N	$Furin^{tm1Ajmr}$	9811571	Absent vitelline blood vessels Cardia bifida
		FES	NA	C, T, Mo, He, G, Im, Ey, Ho, N, D, Mu, Rp	Fes^{tm2Mcs}	11977979	Abnormal vasculogenesis and heart morphology Hemorrhage

Data from International Knockout Mouse Consortium (IKMC) database accessed 12/9/2011, PMID 21677750 Skarnes *et al*., Nature 2011, Jun 15;474(7351):337-42
E = Embryonic day, NA = Not Available

Affected Anatomical systems key: Adipose[A], Behaviour[B], Cardiovascular[C], Cellular[Ce], Digestive/alimentary[D], Embryogenesis[Em], Endocrine/exocrine[En], Eye[Ey], Growth/size[G], Haemapoetic[He], Homeostasis/metabolic[Ho], Immune[Im], Integument[Int], Liver/biliary system[L], Mortality/aging[Mo], Muscle[Mu], Nervous system[N], Renal/urinary[Rn], Reproductive[Rp], Respiratory[Rs], Skeleton[S], Tumorigenesis[T,

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Table 7b: Mouse Model Details for Known Loci

					If Cardiovascular or Metabolic genotype		
Lead SNP	Chr	Nearest Gene(s)	Homozygous null Phenotype	Affected Anatomical Systems	Strain/Stock Designation	Reference (PubMed)	Affected systems
rs17465637	1	MIA3	No mouse model	NA	NA		
rs11206510	1	PCSK9	Increased clearance of circulating cholesterol and decreased plasma cholesterol levels	Ho, L	$Pcsk9^{tm1.1Prat}$ $Pcsk9^{tm1.2Prat}$ $Pcsk9^{tm1Jdh}$	18666258 18666258 15805190	Decreased circulating HDL and LDL
rs17114036	1	PPAP2B	No survival past E10.5, defects in extraembryonic vasculogenesis and axis patterning	C, Mo, G, E, Ho, N	$Ppap2b^{tm1Stw}$ $Ppap2b^{tm2Stw}$ $Ppap2b^{tm3.1Stw}$	12925589 17610274	abnormal vasculogenesis hemorrhage abnormal phospholipid level
rs599839	1	PSRC1 SORT1	No phenotype Increased protection from age- and injury-related neuron lose	NA Ce, Ey, Ho, Im, N	NA NA		
rs6725887	2	WDR12	No phenotype	NA			
rs98188708	3	MRAS	Homozygous for insertional mutation that inactivates gene are grossly normal, no morphological or neurological defects; mutant astrocytes	No phenotype			
rs17609940	6	ANKS1A	No mouse model	NA			
rs12526453	6	PHACTR1	No phenotype	NA			
rs2048327	6	SLC22A3 LPAL2 LPA	Normal phenotype No mouse model No mouse model	NA NA NA			
rs12190287	6	TCF21	Hypoplastic lungs and kidneys with abnormal vasculature of these organs and hemopericardium. Die at birth due to respiratory failure. Some mutations are also asplenic. Some alleles cause sex reversal in XY mice.	C, Mo, Ho, Rs, He, R, Im, In, D, M, En	$Tcf21^{tm1Jrt}$	10572052	abnormal lung and kidney vasculature morphology hemopericardium
rs11556924	7	ZC3HC1	No phenotype	NA			
rs579459	9	ABO	No phenotype	NA			
rs1333049	9	CDKN2A	Null mutants of p16INK4a or p19ARF proteins each show increased tumor susceptibility and sensitivity to carcinogens. Loss of both gives very early onset. p19ARF nulls also show thymic hyperplasia and the eye's hyaloid vascular system fails to regress.	T, Int, Ey, Ho, Mo, Em, Rs, N, En, B	NA		

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		CDKN2B	Increased tumor incidence, lymphoid hyperplasia, and extramedullary hematopoiesis	T, Int, Mo, He, Im, En, Rp, Ho	NA		
rs501120	10	CXCL12	Late embryonic lethality, impaired myelopoiesis, abnormal cerebellum development, abnormal germ cell migration, abnormal angiogenesis around the stomach, and ventricular septal defects.	C, N, L, Im, Rp, He, Mo	$Cxcl12^{tm1Tng}$ $Cxcl12^{tm3.1(HBEGF/EGFP)Tng}$	8757135 20850355	Abnormal angiogenesis Perimembraneous ventricular septal defect Liver hemorrhage
rs12413409	10	CYP17A1 CNNM2 NT5C2	Early embryonic lethality No phenotype No phenotype	Ho, B, N, Rp, Mo			
rs10953541	10	KIAA1462	No mouse model	NA			
rs1412444	10	LIPA	No phenotype	C, Mo, L, Im, Ho, A, D, En, R, G, He, B, Rs, N, Int	$Lipa^{tm1Ggb}$	9700186	abnormal liver sinusoid morphology increased circulating insulin level, insulin resistance decreased circulating HDL, increased LDL, free fatty acid
rs974819	11	PDGFD	No phenotype	NA			
rs964184	11	ZNF259 APOA5 APOA1	No mouse model Increased triglyceride and VLDL cholesterol levels Reduced HDL, non-HDL cholesterol, and cholesterol ester levels, increased plasma triglyceride and free cholesterol levels, impaired corticosteroid synthesis	NA Ho C, Ho, He, Im, Ce, L, En	$Apoa5^{tm1Hgc}$ $Apoa1/Apoc3/Apoa4^{tm1Hmez}$ $Apoa1^{tm1Unc}$	11588264 16497661 1496008	increased circulating VLDL, triglyceride increased susceptibility to atherosclerosis abnormal blood vessel healing decreased cholesterol efflux decreased circulating HDL, LDL, VLDL, increased circulating triglyceride
rs2258916	12	HNF1A C12orf43	Die at 3-6 weeks from progressive wasting syndrome, liver and renal dysfunction and type II diabetes. Mutants have little or no phenylalanine hydroxylase, albumin, alpha 1-antitrypsin and secreted insulin No mouse model	Mo, G, Ho, L	$Hnf1a^{tm1.1Ylee}$ $Hnf1a^{tm1Mya}$ $Hnf1a^{tm2Mya}$ $Hnf1a^{tm2Ylee}$	9566924 8598044 8598044 12529398	Increased cholesterol level decreased circulating insulin/ hyperglycaemia
rs3184504	12	SH2B3	No phenotype	He, Im, Ce			
rs4773144	13	COL4A1 COL4A2	Various eye and vision defects. Newborn mutants may also exhibit bruises Variable phenotype affecting the eye, brain and vascular stability	C, V, Mo, G, Em, N, Ho, R C, N, Ho, G, Em, V, He, Mo	$Col4a1/Col4a2^{tm1Epo}$ $Col4a1^{Bru}$ $Col4a1^{deltaex40}$ $Col4a1^{ENU4004}$ $Col4a1^{ENU911}$	14998921 15905400 10886015 3724777	dilated vasculature hemopericardium bruising hemorrhage corneal vascularization

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					Col4a1^{Raw} Col4a1^{Svc} Col4a2^{ENU4003} Col4a2^{ENU415}	11929848 11929848 10886015 6877261	
rs2895811	14	HHIPL1	No phenotype	NA			
rs3825807	15	ADAMTS7	No phenotype	NA			
rs12936587	17	RAI1	Usually die as embryos. Survivors have shortened life spans and show severe craniofacial and axial skeleton defects	Mo, S, N, A, Ho, G, B, Rs			
		PEMT	Normal phenotype on normal diets but display liver abnormalities on choline deficient diets or high fat and cholesterol diets.	N, L, Ho, G, En, B, Mo	Pemt^{tm1J}	9371769	decreased circulating HDL
		RASD1	Reduced ability to entrain to low intensity light with resulting abnormalities in circadian rhythm.	B			
rs216172	17	SMG6	No phenotype	NA			
rs46522	17	UBE2Z	No phenotype	NA			
rs1122608	19	LDLR	2X higher total plasma cholesterol and 7-9X higher IDL and LDL levels on a normal diet compared to controls. On a high cholesterol diet, mutant effects dramatically increase and mice develop xanthomatosis and atherosclerosis.	C, Ho, N, A, G, Im, L, B, He, En, In, Ey, Mo, Mu, Ce	Ldlr^{tm1Her} Ldlr^{Hlb301} Ldlr$^{tm1(LDLR)Mae}$	8349823 11076954	Multiple different abnormal morphologies Arteriosclerosis Aortic aneurysm Artery occlusion Altered response to myocardial infarction increased and decreased circulating HDL, VLDL, triglyceride decreased circulating LDL
rs2075650	19	APOE	Mutations at this locus cause diet-induced hypercholesterolemia and atherosclerosis. Mutants also develop foam-cell rich deposits in proximal aorta, impaired blood-nerve and blood-brain barriers, and many xanthomatous lesions.	C, Ho, N, Rn, Mu, L, A, G, En, D, Ce,B, Im, Rs, Rp, S, Ey, He, Mo, Int	Apoe$^{tm1(APOE)Kyan}$ Apoe$^{tm1(APOE)Sfu}$ Apoe$^{tm1(APOE*2)Mae}$ Apoe^{shl} Apoe$^{Tg(rtTA)1Gaga}$ Apoe^{tm1Khw} Apoe^{tm1Lmh}	11930145 10655544 9649566 10087291 18464897 11792702 7840811	Abnormal circulating cholesterol levels (increased and decreased LDL, HDL, VLDL and triglyceride levels) atherosclerotic lesions
rs9982601	21	gene_desert KCNE2	No phenotype Stomach hyperplasia and achlorhydria	NA D, Ho			

Data from International Knockout Mouse Consortium (IKMC) database accessed 25/10/2011, PMID 21677750 Skarnes *et al*., Nature 2011, Jun 15;474(7351):337-42
E = Embryonic day, NA = Not Available
Affected Anatomical systems key: Adipose^{A}, Behaviour^{B}, Cardiovascular^{C}, Cellular^{Ce}, Digestive/alimentary^{D}, Embryogenesis^{Em}, Endocrine/exocrine^{En}, Eye^{Ey}, Growth/size^{G}, Haemapoetic^{He}, Homeostasis/metabolic^{Ho}, Immune^{Im}, Integument^{Int}, Liver/biliary system^{L}, Mortality/aging^{Mo}, Muscle^{Mu}, Nervous system^{N}, Renal/urinary^{Rn}, Reproductive^{Rp}, Respiratory^{Rs}, Skeleton^{S}, Tumorigenesis^{T,}

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Supplementary Table 8: Risk Factors

Locus	RSID	SNP	CAD P-value	Risk factor summary	Global Lipids Genetics Consortium P-value and Effect Direction				ICBP P-value		MAGIC P-value and Effect Direction					DIAGRAM P-value and Effect Direction		GIANT P-value	
				Trait n	TC 97743	LDL-C 93070	HDL-C 97527	TG 94244	SBP 69395	DBP 69395	FG 46186	FI 38238	2hG 15234	H-B 36466	H-IR 37037	T2D NA		BMI 122483	WHR 76191
Additional Loci																			
IL6R	rs4845625	T/C	3.55 E-08	None	5.79 E-01 +	5.51 E-01 +	5.61 E-01 +	5.74 E-01 +	2.68 E-01	2.01 E-01	7.84 E-01 +	9.14 E-01 -	2.25 E-01 +	9.29 E-01 -	7.25 E-01 +	6.36 E-01	+	9.33 E-01	3.40 E-01
APOB	rs515135	C/T	4.80 E-10	LDL-C, TC	8.38 E-92 +	3.14 E-109 +	9.13 E-03 -	6.66 E-04 +	6.43 E-01	1.00 E-01	3.54 E-01 -	9.68 E-01 +	6.63 E-01 +	9.74 E-01 -	8.84 E-01 -	1.50 E-01	-	9.95 E-01	3.20 E-01
ABCG5/ ABCG8	rs6544713	T/C	8.72 E-10	LDL-C, TC	1.17 E-44 +	2.37 E-47 +	1.61 E-01 -	4.22 E-03 +	8.99 E-01	8.98 E-01	3.73 E-01 -	4.50 E-01 +	7.91 E-02 +	2.00 E-01 +	5.32 E-01 +	2.27 E-01	-	1.24 E-01	4.40 E-01
GGCX/ VAMP10/ VAMP8	rs1561198	T/C	4.48 E-09	None	7.48 E-02 -	1.30 E-01 -	4.63 E-01 -	8.19 E-01 +	9.85 E-01	9.52 E-01	6.27 E-02 -	8.46 E-01 -	9.67 E-01 +	1.71 E-01 +	9.84 E-01 -	5.55 E-01	+	1.25 E-01	3.50 E-01
ZEB2-AC074093.1	rs2252641	C/T	3.66 E-08	None	7.29 E-01 +	2.31 E-01 +	1.31 E-01 +	1.96 E-01 -	1.90 E-02	3.14 E-02	8.17 E-01 +	5.61 E-01 -	6.58 E-01 +	3.84 E-01 -	6.86 E-01 -	3.84 E-03	-	8.41 E-01	9.00 E-01
EDNRA	rs1878406	T/C	1.32 E-13*	None	3.76 E-01 +	4.93 E-01 +	8.87 E-01 +	7.21 E-01 -	8.82 E-02	8.08 E-01	1.04 E-01 -	3.98 E-01 -	1.08 E-01 -	3.87 E-01 +	5.32 E-01 -	NA	NA	6.22 E-01	3.50 E-01
GUCY1A3	rs7692387	G/A	4.57 E-09	DBP	2.94 E-01 +	8.27 E-01 +	7.63 E-01 +	2.47 E-01 +	6.05 E-03	3.35 E-05	1.85 E-01 +	6.67 E-01 -	8.27 E-01 -	6.24 E-01 -	9.67 E-01 -	5.20 E-02	+	6.21 E-01	9.50 E-01
SLC22A4/ SLC22A5	rs273909	G/A	1.43 E-08	None	3.04 E-03 +	3.60 E-04 +	2.89 E-02 -	1.94 E-02 +	8.80 E-01	4.71 E-01	2.45 E-01 -	8.27 E-01 +	9.70 E-01 +	2.70 E-01 +	8.15 E-01 +	6.87 E-01	+	4.50 E-01	2.30 E-01
KCNK5	rs10947789	T/C	1.63 E-08	None	1.76 E-01 -	5.05 E-01 -	2.55 E-02 -	8.80 E-01 +	6.24 E-01	1.70 E-02	6.99 E-01 -	3.60 E-01 +	7.70 E-02 -	5.54 E-01 +	4.94 E-01 +	3.92 E-01	-	1.92 E-01	2.70 E-02
PLG	rs4252120	T/C	5.00 E-09	None	5.78 E-01 +	3.39 E-01 +	6.65 E-01 -	9.10 E-01 +	7.35 E-01	7.32 E-01	2.03 E-01 +	6.91 E-01 +	6.89 E-01 -	9.01 E-01 +	3.94 E-01 +	9.31 E-01	-	6.75 E-02	6.80 E-02
HDAC9	rs2023938	T/C	3.59 E-10*	None	5.17 E-01 +	5.23 E-01 +	9.77 E-01 -	6.24 E-01 -	1.41 E-02	7.32 E-01	8.44 E-01 -	8.05 E-01 -	7.82 E-02 -	5.24 E-01 -	8.19 E-01 -	7.05 E-01	+	9.29 E-01	7.00 E-01
LPL	rs264	G/A	5.06 E-09	HDL-C, TG	6.73 E-01 +	4.55 E-01 +	7.02 E-48 -	5.66 E-46 +	9.84 E-01	7.94 E-01	1.29 E-01 +	6.60 E-01 +	6.23 E-01 +	5.30 E-01 -	5.02 E-01 +	5.54 E-02	+	2.10 E-02	9.80 E-01
TRIB1	rs2954029	A/T	4.53 E-08	TG, TC, LDL-C, HDL-C	1.17 E-35 +	5.36 E-29 +	4.85 E-18 -	3.29 E-55 +	3.75 E-01	7.53 E-01	6.37 E-01 -	6.40 E-01 +	1.34 E-02 +	9.50 E-01 +	8.71 E-01 +	9.57 E-01	+	3.59 E-01	3.50 E-01
FLT1	rs9319428	A/G	1.01 E-08	None	4.77 E-01 +	6.46 E-01 -	1.02 E-01 +	5.87 E-01 +	8.39 E-01	1.05 E-01	6.69 E-01 -	9.35 E-01 +	7.80 E-01 -	4.22 E-01 +	8.52 E-01 +	9.26 E-01	+	3.76 E-01	3.20 E-03
FURIN/ FES	rs17514846	A/C	4.49 E-10	SBP	7.19 E-01 +	1.37 E-01 +	3.14 E-01 +	1.02 E-01 -	1.17 E-05	4.32 E-03	5.02 E-01 +	5.64 E-01 -	8.52 E-01 +	6.04 E-01 -	5.26 E-01 -	1.33 E-01	+	1.16 E-01	5.70 E-02
Established Loci																			
MIA3	rs17465637	C/G	n/a	None	2.38 E-01 -	1.99 E-01 -	5.12 E-01 +	7.72 E-02 -	5.90 E-01	9.82 E-01	3.33 E-01 -	3.27 E-01 +	NA NA	3.36 E-01 +	4.47 E-01 +	3.24 E-01	+	2.50 E-01	2.10 E-01

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PCSK9	rs11206510	T/C	1.79 E-05	TC, LDL-C	3.54 E-20	+	5.23 E-20	+	1.90 E-01	-	2.07 E-04	+	8.63 E-01	2.78 E-01	5.93 E-01	-	1.45 E-01	-	1.98 E-01	-	3.19 E-01	-	1.07 E-01	-	4.51 E-02	+	5.53 E-01	1.50 E-01
PPAP2B	rs17114036	C/T	5.80 E-12	None	8.09 E-01	+	7.47 E-01	-	2.54 E-02	+	2.92 E-01	-	4.01 E-01	7.19 E-01	9.40 E-01	-	5.64 E-01	-	8.13 E-01	-	6.84 E-01	-	5.81 E-01	-	NA	NA	5.08 E-01	8.60 E-01
SORT1	rs599839	A/G	3.85 E-15	LDL-C, TC, HDL-C	4.12 E-130	+	2.94 E-168	+	5.56 E-07	-	4.43 E-02	+	8.91 E-01	6.59 E-01	1.25 E-01	-	2.65 E-01	-	1.11 E-01	-	8.68 E-01	+	2.15 E-01	-	6.11 E-02	-	4.71 E-02	1.70 E-01
WDR12	rs2351524	T/C	1.88 E-17	None	4.51 E-04	-	2.49 E-03	-	4.55 E-01	-	4.82 E-02	-	9.49 E-01	1.08 E-01	6.85 E-02	-	1.90 E-01	+	5.50 E-01	+	1.03 E-01	+	2.92 E-01	+	9.60 E-02	-	1.99 E-02	3.10 E-01
MRAS	rs9818870	T/C	2.62 E-09	None	1.25 E-01	+	3.04 E-01	+	6.58 E-01	-	3.50 E-01	+	3.92 E-02	2.19 E-02	5.46 E-01	+	1.65 E-01	+	1.54 E-01	+	3.25 E-01	+	1.83 E-01	+	5.96 E-01	+	3.85 E-01	3.00 E-01
ANKS1A	rs12205331	C/T	4.18 E-05	None	8.00 E-01	+	6.43 E-01	+	8.84 E-04	-	5.29 E-03	+	2.85 E-01	9.20 E-02	3.28 E-01	+	7.37 E-01	+	8.98 E-01	+	8.12 E-01	+	5.09 E-01	+	2.36 E-01	+	1.28 E-01	7.60 E-01
ANKS1A	rs3822921	A/G	6.17 E-05	TC, Height, HDL-C	2.61 E-06	-	2.75 E-04	-	1.65 E-05	-	7.68 E-01	-	6.85 E-01	4.09 E-01	7.97 E-01	+	6.07 E-02	+	2.56 E-01	-	1.57 E-01	+	1.39 E-01	+	3.15 E-01	+	1.13 E-02	3.90 E-01
ANKS1A	rs12525532	T/C	4.76 E-04	FI, H-IR	1.32 E-03	-	1.52 E-02	-	1.02 E-03	-	2.14 E-02	+	6.01 E-01	7.64 E-01	2.41 E-03	+	1.20 E-05	+	4.45 E-01	-	1.21 E-02	+	1.83 E-05	+	1.95 E-01	+	1.34 E-01	4.80 E-01
PHACTR1	rs9369640	A/C	7.53 E-22	None	1.55 E-01	-	1.75 E-01	-	4.78 E-01	+	1.02 E-01	-	1.72 E-02	2.45 E-02	2.76 E-01	+	8.44 E-01	-	5.01 E-04	-	5.38 E-01	-	8.78 E-01	-	6.38 E-01	+	4.78 E-02	7.10 E-01
SLC22A3/ LPAL2/ LPA	rs3120139	A/G	2.23 E-07	TC, LDL-C	5.24 E-07	+	4.03 E-05	+	6.39 E-01	-	4.29 E-04	+	9.21 E-01	3.40 E-01	5.45 E-02	+	9.22 E-01	+	7.82 E-01	-	1.48 E-01	-	8.67 E-01	+	3.88 E-01	-	2.08 E-01	4.40 E-02
SLC22A3/ LPAL2/ LPA	rs2048327	C/T	6.86 E-11	None	5.95 E-04	+	4.07 E-03	+	4.89 E-01	-	1.49 E-02	+	4.72 E-01	4.94 E-01	3.97 E-02	+	4.32 E-01	-	4.12 E-01	-	6.41 E-02	-	9.15 E-01	-	7.24 E-01	-	1.18 E-02	3.40 E-01
TCF21	rs2327429	T/C	3.04 E-11	None	2.38 E-03	-	7.18 E-03	-	2.99 E-01	-	8.57 E-01	-	2.76 E-01	1.55 E-01	7.81 E-01	+	1.57 E-01	-	5.54 E-01	+	4.48 E-02	-	1.59 E-01	-	9.79 E-01	-	1.45 E-01	1.60 E-01
ZC3HC1	rs11556924	C/T	6.74 E-17	DBP	1.58 E-01	+	2.93 E-02	+	3.77 E-03	-	1.81 E-01	+	1.27 E-04	1.79 E-05	8.92 E-02	+	3.78 E-01	+	8.54 E-02	+	5.63 E-01	-	4.16 E-01	+	3.52 E-01	+	6.28 E-02	8.30 E-01
ABO	rs579459	C/T	2.66 E-08	LDL-C, TC	4.03 E-20	+	2.36 E-21	+	8.39 E-02	+	1.49 E-02	-	1.91 E-01	1.03 E-03	4.54 E-03	+	5.86 E-01	+	6.30 E-01	+	1.07 E-01	-	5.27 E-01	+	3.40 E-01	+	7.75 E-01	3.40 E-01
CDKN2BAS	rs1333049	C/G	1.39 E-52	None	8.13 E-03	-	1.56 E-01	-	2.62 E-01	-	7.11 E-01	-	9.93 E-01	1.75 E-01	4.16 E-02	+	6.61 E-01	+	3.97 E-02	+	3.40 E-01	+	2.77 E-01	+	5.17 E-02	+	6.36 E-01	1.30 E-01
CXCL12	rs2047009	G/T	1.59 E-09	None	8.90 E-01	+	6.75 E-01	+	6.78 E-01	+	6.58 E-01	-	6.74 E-01	2.13 E-02	8.50 E-01	+	3.90 E-01	+	6.68 E-01	+	6.70 E-01	+	3.82 E-01	+	5.39 E-01	+	7.22 E-01	1.80 E-01
CXCL12	rs687175	T/C	2.31 E-09	None	1.94 E-01	-	5.23 E-01	-	7.38 E-01	-	1.41 E-01	-	5.12 E-01	1.23 E-01	7.53 E-02	-	1.56 E-01	-	9.93 E-01	+	5.22 E-01	-	1.29 E-01	-	6.88 E-01	-	5.08 E-01	4.20 E-02
CYP17A1/ CNNM2/ NT5C2	rs12413409	G/A	6.26 E-08	SBP, DBP, BMI	1.24 E-01	+	7.64 E-01	+	1.76 E-01	+	4.37 E-01	+	2.00 E-09	8.81 E-06	8.68 E-01	-	9.78 E-01	-	3.55 E-01	+	7.36 E-01	-	9.56 E-01	-	7.35 E-01	-	4.75 E-05	5.00 E-02
KIAA1462	rs2505083	C/T	1.35 E-11	None	3.09 E-01	+	6.03 E-01	+	5.46 E-01	-	6.27 E-02	+	3.93 E-01	1.73 E-01	4.44 E-01	+	3.63 E-01	+	7.50 E-01	+	8.33 E-01	+	3.28 E-01	+	3.17 E-01	+	6.96 E-01	8.70 E-01

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LIPA	rs11203042	T/C	6.08 E-06	None	6.24 E-01	-	7.14 E-01	-	6.34 E-01	+	5.22 E-02	-	6.88 E-01	5.70 E-01	4.95 E-01	+	2.60 E-01	-	3.08 E-01	-	1.04 E-01	-	1.74 E-01	-	3.72 E-01	-	9.58E-01	3.80 E-01
LIPA	rs2246833	T/C	9.49 E-06	None	8.70 E-01	-	6.59 E-01	-	1.58 E-01	+	5.22 E-01	-	3.91 E-01	6.08 E-01	3.29 E-01	+	2.81 E-01	-	1.70 E-01	-	2.61 E-01	-	4.83 E-01	-	6.33 E-01	-	1.77 E-01	2.90 E-01
PDGFD	rs974819	T/C	3.55 E-11	None	3.42 E-01	+	2.71 E-01	+	3.83 E-01	-	3.19 E-01	+	9.91 E-01	7.57 E-01	2.32 E-02	+	4.97 E-01	+	5.29 E-01	+	3.43 E-01	-	4.88 E-01	+	4.04 E-01	+	7.23 E-01	8.10 E-01
ZNF259/ APO5A/ APOA1	rs9326246	C/G	1.51 E-07	TG, TC, HDL-C, LDL-C	7.09 E-32	+	9.99 E-15	+	1.79 E-19	-	4.7 E-124	+	3.18 E-01	6.71 E-01	3.24 E-02	+	7.90 E-01	+	3.35 E-01	+	8.00 E-01	-	4.69 E-01	+	2.31 E-01	+	2.96 E-01	5.20 E-01
SH2B3	rs3184504	T/C	5.44 E-11	DBP, TC, SBP, LDL-C, HDL-C	2.69 E-11	-	1.73 E-09	-	4.97 E-06	-	1.85 E-01	+	1.69 E-09	2.33 E-14	4.09 E-01	+	7.51 E-01	+	1.12 E-01	+	8.57 E-01	+	5.20 E-01	+	3.37 E-01	+	1.30 E-04	9.00 E-01
COL4A1/ COL4A2	rs9515203	T/C	5.85 E-12	None	2.14 E-01	-	4.57 E-01	-	6.31 E-01	+	1.17 E-01	-	1.45 E-03	1.12 E-02	3.42 E-01	-	2.58 E-01	+	6.70 E-02	-	1.14 E-01	+	4.16 E-01	+	7.55 E-02	-	3.64 E-02	2.20 E-01
COL4A1/ COL4A2	rs3809346	A/G	2.56 E-12	None	1.55 E-02	-	1.26 E-02	-	5.79 E-01	-	3.61 E-01	+	6.01 E-01	7.54 E-01	1.04 E-01	-	4.64 E-01	+	4.73 E-02	+	5.30 E-02	+	4.69 E-01	+	3.87 E-01	-	1.71 E-01	2.60 E-01
HHIPL1	rs2895811	C/T	4.08 E-10	None	7.95 E-02	+	5.41 E-02	+	7.47 E-01	+	8.84 E-01	+	1.78 E-01	7.62 E-01	2.12 E-01	-	8.65 E-01	+	9.53 E-01	+	6.27 E-01	+	9.76 E-01	-	1.40 E-01	-	7.73 E-01	2.20 E-01
ADAMTS7	rs3825807	A/G	n/a	None	6.92 E-01	+	7.98 E-01	-	5.96 E-01	+	8.38 E-01	-	6.89 E-01	2.46 E-01	4.77 E-01	-	5.20 E-01	-	4.65 E-01	-	4.65 E-01	-	4.85 E-01	-	NA	NA	2.40 E-01	1.90 E-01
ADAMTS7	rs11072794	T/C	1.10 E-12	None	9.55 E-01	-	3.31 E-01	-	3.41 E-01	+	6.82 E-01	-	2.79 E-01	1.69 E-03	5.07 E-01	+	8.80 E-01	-	2.51 E-01	+	7.21 E-01	-	9.89 E-01	+	4.86 E-02	+	2.91 E-01	5.50 E-01
RAI1/ PEMPT/ RASD1	rs12936587	G/A	1.24 E-09	WHR	2.26 E-01	+	3.23 E-01	+	1.69 E-02	-	9.59 E-03	+	8.70 E-01	6.13 E-01	4.50 E-01	-	8.20 E-01	-	5.21 E-01	+	4.09 E-01	+	7.11 E-01	-	5.80 E-01	+	3.09 E-01	2.86 E-05
SMG6	rs2281727	G/A	7.83 E-09	None	9.72 E-03	-	9.18 E-02	-	1.24 E-02	-	8.60 E-01	-	3.94 E-01	6.75 E-01	3.60 E-01	-	3.33 E-01	-	6.34 E-01	-	5.39 E-01	-	3.02 E-01	-	7.21 E-01	-	2.16 E-02	1.40 E-01
UBE2Z	rs15563	G/A	9.37 E-06	Height	8.69 E-01	+	3.26 E-01	+	1.15 E-01	-	7.13 E-01	-	7.22 E-01	1.41 E-01	9.56 E-01	+	1.13 E-01	-	3.84 E-01	+	7.59 E-02	-	2.31 E-01	-	1.31 E-03	+	6.22 E-01	8.10 E-02
LDLR	rs1122608	G/T	6.33 E-14	LDL-C, TC	4.59 E-26	+	1.24 E-33	+	2.87 E-01	-	3.64 E-01	+	9.46 E-01	6.65 E-01	6.90 E-01	-	4.61 E-01	-	4.10 E-02	+	8.44 E-01	-	5.19 E-01	-	7.23 E-01	-	1.28 E-01	3.70 E-01
APOE	rs2075650	G/A	5.86 E-11**	LDL-C, TC, TG, HDL-C	1.33 E-84	+	3.76 E-110	+	1.10 E-16	-	1.31 E-19	+	4.86 E-01	9.52 E-01	6.35 E-01	-	9.49 E-01	-	1.24 E-02	-	7.73 E-01	-	9.35 E-01	-	8.54 E-01	+	2.37 E-02	2.50 E-02
KCNE2	rs9982601	T/C	7.67 E-17	None	8.64 E-01	+	4.13 E-01	-	8.55 E-02	+	2.94 E-01	+	1.11 E-01	2.59 E-01	8.75 E-01	+	5.07 E-01	-	9.80 E-01	-	6.96 E-01	-	9.71 E-01	-	2.00 E-01	-	4.27 E-01	2.10 E-01

SNP : Effect/ Non Effect Allele, CAD P-value (for Stage 1 and 2 analysis, unless * Stage 1, 2 and 3 combined P, ** Stage 2 results only, n/a Not on Metabochip), Risk factor summary : Summary of significant risk factors (in order of significance), TC : Total Cholesterol level, LDL-C : Low Density Lipoprotein Cholesterol level, HDL-C : High Density Lipoprotein Cholesterol level, TG : Triglyceride level, SBP : Systolic Blood Pressure, DBP : Diastolic Blood Pressure, FG : Fasting glucose level, FI : Fasting Insulin level, 2hG : 2 hour glucose level, H-B : HOMA-B level, H-IR : HOMA-IR level, T2D : Type 2 Diabetes, BMI : Body Mass Index, WHR : Waist Hip Ratio (BMI adjusted), n values quoted for each trait are the average of the 51 SNPs within the table. Red shaded squares highlight P-values less than the Bonferroni significance level of 6.5E-05 which was based on 51 SNPs and 15 traits.

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Supplementary Table 9: SNPs at an FDR≤5% and LD threshold of r2 < 0.2 used in estimating heritability
Provided as separate attachment

Supplementary Table 10: Network molecules

Provided as separate attachment

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1. Study characteristics

Descriptions of all studies in stage 1 (CARDIoGRAM discovery) are given in ref 1[1]. **Supplementary Table 2a/b** provides an overview of the Stage 2 and 3 studies. A more detailed description of each study is given below:

Stage 2 Studies

ADVANCE

The ADVANCE (Atherosclerotic Disease, Vascular Function, and Genetic Epidemiology) study is a case-control investigation of genetic and nongenetic determinants of CAD and mode of CAD presentation. All study participants have been identified and recruited from the membership of Kaiser Permanente of Northern California (KPNC), a large integrated health care delivery system in the San Francisco Bay area and surrounding counties The ADVANCE Study was approved by the Institutional Review Board at Stanford and the Kaiser Foundation Research Institute. All subjects gave written informed consent
The phenotype for cases was program members aged 45 years or older for males and 55 years or older for females at the time of their incident clinical coronary artery disease event between 28 October 2001 and 31 December 2003. For MI, patients had to have positive cardiac enzymes in the electronic databases as well as a primary discharge diagnosis of myocardial infarction (ICD 9 code 410). For stable angina, patients had to have diagnosis of stable angina (ICD9 code 413.x) in the electronic outpatient databases followed by confirmation from both the primary care physician and the patient of the recent onset of incident stable and typical angina. Two cases from the early onset CAD cohort (age of onset of CAD < 45 years for men and < 55 years for women) not included in prior ADVANCE GWAS were also genotyped. The control phenotype was defned as Program members aged 60 to 69 as of January 6, 2001, with no history of cardiovascular disease, cancer (other than nonmelanoma skin cancer), renal failure, liver cirrhosis, dementia, or human immunodeficiency virus/ acquired immunodeficiency syndrome or with a source of care greater than 50 miles (80.47 km) from the clinic used for data collection were recruited[2-5].

AMC-PAS/ SANGUIN

The AMC-PAS(Academic Medical Center Amsterdam Premature Atherosclerosis Study) study consists of patients referred to the Academic Medical Center in Amsterdam, which is specialised in premature CAD, for investigation of symptomatic coronary and/or peripheral arterial disease. Case definition was symptomatic CAD before the age of 51 years, defined as MI, coronary revascularization, or evidence of at least 70% stenosis in a major epicardial artery
Controls were blood donors from the north-west region of the Netherlands; recruited at routine Sanquin Blood Bank donation sessions. More than 95% of the controls are from the same region as the cases of the AMC-PAS cohort[6].

Angio-Lueb/KORA F3

The Lübeck Registry of Structural Heart Disease /KORA (Kooperative Gesundheitsforschung in der Region Augsburg) survey S3/F3 datasets included cases selected from consecutive patients referred for coronary angiography, which were classified as CAD/MI based on the coronary angiogram; cases were < 65 y in males or < 70 y in females. The KORA survey contains representative samples from the general population living in or near Augsburg, Germany and were conducted between 1994 and 2004[1,7].

Cardiogenics

The Cardiogenics Study recruited patients from five European centres. Patients from Germany(Lubeck and Regensburg) and the UK (Leicester) were under the age of 65 with a confirmed primary MI within the

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preceding 3-36 months. Exclusion criteria were (*i*) a history of diabetes mellitus based on plasma glucose >7.0 mmol/l or HbA1C > 7.0 (*ii*) renal insufficiency, (*iii*) patients not on statin therapy, (*iv*) CRP level >10mg/dl, (v) patients not fasting at the time of blood sampling or (*vi*) current smokers. The French (Paris) cohort comprised patients aged 33 to 87, recruited within the BAAAC (Banque d'ADN et d'ARN de patients présentant une Athérosclérose Coronarienne) study, with symptoms of acute coronary syndrome who had one stenosis >50% diagnosed in at least one major coronary artery.
Controls comprised healthy individuals (aged 32 to 65 years) recruited in the UK(Cambridge) who were blood donors recruited as part of the Cambridge Bioresource[8].

DILGOM

Samples were collected as part of the Dietary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) study. Study participants were aged 25–74 years and were drawn from five geographical areas of Finland. All CAD cases are incident definite or possible MI or coronary death, or unstable angina during follow-up, coronary revascularization during follow-up, documented MI at baseline, or an unclassifiable coronary death during follow-up. MI cases had definite myocardial infarction. Non-cases were selected from the same population-based longitudinal cohort study[9].

DUKE

The Duke CATHGEN biorepository consists of subjects recruited sequentially through the cardiac catheterization laboratories at Duke University Medical Center (Durham, NC, USA). After informed consent was obtained, blood was drawn from the femoral artery at the time of arterial access for catheterization. Clinical data were provided by the Duke Databank for Cardiovascular Disease (DDCD), a database of patients undergoing catheterization at Duke University since 1969. Follow-up data, including occurrence of myocardial infarction (MI) and death, were collected at 6 months after catheterization and annually thereafter. Vital status was confirmed through the National Death Index. The Duke Institutional Review Board approved the protocols for CATHGEN. Subjects (case and control), were excluded if they had severe pulmonary hypertension or congenital heart disease or were diabetic.Cases had at least one epicardial coronary vessel with at least 50% blockage, age of onset was no older than 65 for women and 55 for men. Controls were required to be at least 50 years old and have no epicardial coronary vessel with greater than 30% blockage. Controls with a history of ICC/PCI, CABG, MI or transplant were excluded[10].

EGCUT

The EGCUT (Estonian Genome Center of University of Tartu) study recruited samples from Estonia. Cases were study participants who reported following cardiovascular disease events (ICD10 I20-I26) when recruited. Controls were participants in the same study that did not those cardiovascular disease events[11].

EPIC

The EPIC (European Prospective Study into Cancer and Nutrition) study sub-cohorts from the UK were used, subjects were collected in collaboration with general practicioners, mainly in Cambridgeshire and Norfolk. Cases were individuals who developed a fatal or non-fatal CAD during an average follow-up of 11 years, until June 2006. Participants were identified if they had a hospital admission and/or died with CAD as the underlying cause. CAD was defined as cause of death codes ICD9 410-414 or ICD10 I20-I25, and hospital discharge codes ICD10 I20.0, I21, I22 or I23 according to the International Classification of Diseases, 9th and 10th revisions. Controls were study participants who remained free of any cardiovascular disease during follow-up (defined as ICD9 401-448 and ICD10 I10-I79). Controls were matched to each case by sex, age (within 5 years), and time of enrolment (within 3 months).

FGENTCARD

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The FGENTCARD (Functional Genomic Diagnostic Tools for Coronary Artery Disease) study subjects consisted of 6517 individuals who underwent cardiac catheterization following a single consistent and stringent recruitment protocol between August, 2007 and March 2011 at several hospitals in Lebanon. Catheterization was prompted for myocardial infarction (MI) (12.5%) as diagnosed by electrocardiogram and high troponin levels, unstable angina (27.5%), or other reasons, such as stable angina, or heart failure, or reversible ischemia by stress testing (59.9%). All patients underwent coronary catheterization by Judkins technique. The four main coronary arteries: the left main artery (LMCA), the left anterior descending artery (LAD), the left circumflex artery (LCx), and the right coronary artery (RCA) were visualized from different angles by angiography. The extent of stenosis in these vessels was assessed and recorded by percentage. Cases were defined as follows: Mildly diseased if at least one of the four vessels has less than 50% stenosis, severly diseased if any of the four vessels has ≥50% stenosis. Controls are subjects with no stenosis in the 4 main vessels

FRISCII/GLACIER

The FRISC II, (Fragmin and Fast Revascularization during Instability in Coronary Artery Disease) study was a prospective, randomised, multicentre trial (58 hospitals in Sweden, Norway and Denmark) with parallel groups to compare invasive and non-invasive treatments. FRISCII patients were eligible for inclusion if they had symptoms of ischaemia that were increasing or occurring at rest, or that warranted the suspicion of acute myocardial infarction, with the last episode within 48 h before the start of dalteparin or standard heparin treatment. Myocardial ischaemia had to be verified by electrocardiography (ST depression ≥0·1 mV or T-wave inversion ≥0·1 mV) or by raised biochemical markers (creatine kinase [CK]-MB >6 ug/L, troponin-T >0·10 ug/L, qualitative troponin-T test positive, or catalytic activity of CK, CK-B, or CK MB higher than the local diagnostic limit for myocardial infarction). Exclusion criteria were raised risk of bleeding episodes, anaemia, or indication for or treatment in the past 24 h with thrombolysis, angioplasty in the past 6 months, being on a waiting list for coronary revascularisation, other acute or severe cardiac disease, renal or hepatic insufficiency, known clinically relevant osteoporosis, other severe illness, hypersensitivity to randomised drugs, anticipated difficulties with cooperation or participation in this or another clinical trial[12]. The GLACIER (Gene x Lifestyle interactions And Complex traits Involved in Elevated disease Risk) cohort was used in these analyses as a comparison cohort for FRISCII. GLACIER is a subset of the Västerbottens Intervention Project, a population-based cohort from northern Sweden. The GLACIER cohort is comparable to the full VIP cohort in demographic, anthropometric, and lifestyle characteristics[13].

GoDARTS

The GoDARTS (Genetics of Diabetes Audit and Research in Tayside Scotland) study is a joint initiative of the Department of Medicine and the Medicines Monitoring Unit (MEMO) at the University of Dundee, the diabetes units at three Tayside healthcare trusts (Ninewells Hospital and Medical School, Dundee; Perth Royal Infirmary; and Stracathro Hospital, Brechin), and a large group of Tayside general practitioners with an interest in diabetes care. Cases were a first-ever CAD event, defined as fatal and non-fatal myocardial infarction, unstable angina or coronary revascularisation. Controls were free of coronary artery disease, stroke and peripheral vascular disease[14].

HPS

The MRC/BHF Heart Protection Study (HPS) was a large UK-based cholesterol-lowering trial involving participants with a history of MI, unstable or stable angina, coronary artery bypass grafting, or angioplasty (as well as patients with prior history of stroke or hypertension). HPS CAD cases were compared with population controls from the UK Twins Study and the WTCCC2 National Blood Service Collections[15].

ITH

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The INTERHEART Study (ITH) used worldwide cases and controls of European ethnicity. Cases were incident acute MI, presenting to a hospital within 24 hours of symptom onset, controls were age and sex matched hospital and community based, with no previous diagnosis of heart disease or history of exertional chest pain[16].

LOLIPOP

The LOLIPOP CHD-GEN (London Life Sciences Population) study includes individuals of Indian Asian descent. CHD cases were recruited from the Ealing and Hammersmith hospitals. CAD was defined as a history of MI or coronary artery revascularization (CABG or percutaneous coronary intervention (PCI)), or angiographically confirmed coronary artery stenosis greater than 50%. Clinical diagnosis of MI is based on two out of three of: 1. Chest pain, 2. Raised cardiac enzymes, 3. ECG changes. Controls were Indian Asian men and women, aged 35 to 75 years, without diagnosis or history of CAD and recruited from the lists of 58 General Practitioners in West London. All participants gave written consent for participation in genetic studies and the protocol was approved by the local Research Ethics Committee[17-19].

LURIC/EMIL

The LURIC (LUdwigshafen RIsk and Cardiovascular Health) study inclusion criteria were: German ancestry, clinical stability except for acute coronary syndromes, and the availability of a coronary angiogram. Cases were included with angiographically confirmed CAD (at least one coronary vessel with a stenosis > 50%) The study was approved by the Ethics Committee at the "Aerztekammer Rheinland-Pfalz". Informed written consent was obtained from all participants[20].
The EMIL (Echinococcus Multilocularis and Internal Diseases in Leutkirch study) study is a GerBS control series that consists of healthy, unrelated blood donors recruited between May-July 2004 from the southwestern area of Germany / EMIL controls include population-based non-cases subjects[21].

METSIM

METSIM (METabolic Syndrome In Men) is a population-based cross-sectional study that includes subjects, aged from 45 to 70 years which were randomly selected from the population register of the town of Kuopio in eastern Finland (population 95,000). CAD cases were Angiography-confirmed CAD, myocardial infarction, balloon angioplasty or coronary bypass. Controls were selected from the same population-based sample and were free from MI, coronary angiography, balloon angioplasty, cerebral infarction, cerebral hemorrhage, or any leg operation. The study was approved by the ethics committee of the University of Kuopio and Kuopio University Hospital, and it was in accordance with the Helsinki Declaration[22].

MORGAM

The MORGAM (MONICA, Risk, Genetics, Archiving, and Monograph)Study, has harmonized data from the prospective follow-up of population cohorts in several countries. Finland (FIN): Southern Finland, North Karelia, Kuopio Province, Oulu Province, Turku/Loimaa, Helsinki, France (FRA): Lille, Strasbourg, Toulouse, Germany(GER): Augsburg, Italy(ITA): Brianza and the United Kingdom (UNK): Belfast. All CAD cases are incident definite or possible MI or coronary death, or unstable angina during follow-up, Coronary revascularization during follow-up, Documented MI at baseline, or an unclassifiable coronary death during follow-up. MI cases were:definite myocardial infarction. Controls are 1:1 matched for cases (by age, sex, and region). They are participants who remained free of any cardiovascular disease at the age when the matched case had the first event[23,24].

OHGS

The OHGS (Ottawa Heart Genomics Study) cases had at least one of myocardial infarction, coronary artery bypass graft, percutenaeous intervention or a stenosis of at least 50% in at least one epicardial vessel. Diabetic cases and cases aged greater than 55 for men or 65 for women were excluded. Controls were

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either asymptomatic for cardiovasular disease or had had a CTA or angiogram demonstrating no stenosis of greater than 50%. Controls were required to be at least 65 years old for men and 70 years old for women at the time of recruitment[25].

PIVUS

Individuals within the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) cohort study who developed a fatal or non-fatal myocardial infarction or unstable angina during follow-up were included as cases. Participants were identified as having CHD if they had a hospital admission with CHD as the primary cause of hospitalization and/or died with CAD as the underlying cause. CHD was defined as acute myocardial infarction (ICD-8 and ICD-9 code 410, ICD-10 codes I21-I22) or unstable angina (ICD-8 code 411, ICD-9 code 411B, ICD-10 code I20.0). The positive predictive values (i.e. validity) of the CHD diagnosis in the Swedish hospital discharge register has been demonstrated to be at least 95% when only primary diagnoses are considered. Non-cases were selected from the same longitudinal, community-based cohort study[26].

PopGen

The PopGen Population-based northern German cross-sectional study comprises unrelated CAD patients recruited in Schleswig-Holstein, through the population-based PopGen biobank. Cases had significant CAD (at least a 70% stenosis in one major coronary vessel) with age of onset < 55 y. Population based controls are participants who remained free of any cardiovascular disease[27].

PROCARDIS

The PROCARDIS (European collaborative study of the genetics of precocious coronary artery disease) study is a multi-centre case-control study in which CAD cases and controls were recruited from United Kingdom, Italy, Sweden and Germany. Cases were defined as symptomatic CAD before age 66 years and 80% of cases also had a sibling in whom CAD had been diagnosed before age 66 years. CAD was defined as clinically documented evidence of myocardial infarction (MI) (80%), coronary artery bypass graft (CABG) (10%), acute coronary syndrome (ACS) (6%), coronary angioplasty (CA) (1%) or stable angina (hospitalization for angina or documented obstructive coronary disease) (3%). The cases included 2,136 cases who were half or full siblings. PROCARDIS controls had no personal or sibling history of CAD before age 66 years. PoBI and UK Twin study are population-based controls that were not screened for CAD[28].

PROMIS

PROMIS (The Pakistan Risk Of Myocardial Infarction Study) is an ongoing case-control study of acute myocardial infarction (MI) in urban Pakistan, which by mid-2009 included 5,500 MI cases and 5,500 controls. Cases have typical ECG characteristics, a positive troponin test, and MI symptoms within the previous 24 hours. Controls are individuals frequency-matched to cases by sex and age (in 5 year bands) and identified in the same hospitals as the index cases. Controls have been recruited in the following order of priority: (i) visitors of patients attending the out-patient department; (ii) patients attending the out-patient department for routine non-cardiac complaints, or (iii) non-blood related visitors of index MI cases. A locally-piloted and validated epidemiological questionnaire has been administered to participants by medically qualified research officers that seeks >200 items of information in relation to: ethnicity (eg, personal and paternal ethnicity, spoken language, place of birth and any known consanguinity); demographic characteristics; lifestyle factors (eg, tobacco and alcohol consumption, dietary intake and physical activity); personal and family history of cardiovascular disease; and medication usage. PROMIS has received approval by the relevant research ethics committee of each of the institutions involved in participant recruitment. Informed consent has been obtained from each participant recruited into the study, including consent to use the samples in genetic, biochemical and other analyses[29].

SCARF/SHEEP

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SHEEP/SCARF are Swedish population based case-control studies. Cases are patients with a first confirmed myocardial infarction, controls have no history of myocardial infarction.

STR

The STR (Swedish Twin Registry) registry includes nearly 25,000 pairs of twins of the same sex born in Sweden between 1886 and 1958. Individuals were included within this cohort study who developed a fatal or non-fatal myocardial infarction or unstable angina during follow-up. Participants were identified as having CHD if they had a hospital admission with CHD as the primary cause of hospitalization and/or died with CAD as the underlying cause. CHD was defined as acute myocardial infarction (ICD-8 and ICD-9 code 410, ICD-10 codes I21-I22) or unstable angina (ICD-8 code 411, ICD-9 code 411B, ICD-10 code I20.0). The positive predictive values (i.e. validity) of the CHD diagnosis in the Swedish hospital discharge register has been demonstrated to be at least 95% when only primary diagnoses are considered. Non-cases were selected from the same longitudinal, community-based cohort study. This study was approved by the Ethics Committee of the Karolinska Institute and the Swedish National Data Inspection Authority. All subjects gave informed consent[30].

THISEAS

The THISEAS (The Hellenic Study of Interactions between Snps and Eating in Atherosclerosis Susceptibility) study participants were recruited from 3 hospitals found in the area of Athens. Cases were subjects with a first-ever MI before age of 70 yrs presenting with either ACS or stable CAD defined as >50% stenosis in at least one of the three main coronary vessels assessed by coronary angiography. ACS was defined as acute MI or unstable angina corresponding to class III of the Braunwald classification. ACS patients have also undergone coronary angiography examination that verified the presence of significant stenosis. Controls were subjects age matched without MI/CAD history with negative coronary angiography findings (<30% stenosis), or negative stress test, or subjects without symptoms of disease that were admitted at the same hospitals as cases and were free of any cardiovascular disease, cancer, or inflammatory diseases. Subjects with renal or hepatic disease were excluded from both study groups. The bioethics committee of Harokopio University approved the study and all participants gave their informed consent[31].

ULSAM

The ULSAM (Uppsala Longitudinal Study of Adult Men) is a population-based cohort study of diabetes and cardiovascular disease in men. In 1970, all men born between 1920 and 1924 and residing in Uppsala, Sweden were invited to a health survey at age 50 years. In all, 2322 of 2841 invited men participated (82%). Participants were identified as having CHD if they had a hospital admission with CHD as the primary cause of hospitalization and/or died with CAD as the underlying cause. CHD was defined as acute myocardial infarction (ICD-8 and ICD-9 code 410, ICD-10 codes I21-I22) or unstable angina (ICD-8 code 411, ICD-9 code 411B, ICD-10 code I20.0). The positive predictive values (i.e. validity) of the CHD diagnosis in the Swedish hospital discharge register has been demonstrated to be at least 95% when only primary diagnoses are considered. Non-cases were selected from the same longitudinal, community-based cohort study[32].

WTCCC-CAD2

WTCCC-CAD2 cases comprise patients from four studies: (i) young MI cases with an event below the age of 50 years recruited into the Premature Acute Myocardial Infarction Study (PRAMIS) study[33] (n=214, 85.5% males, mean age at event 42.4±5.8 yrs); (ii) MI cases recruited into The Secondary Prevention of Acute Coronary Events – Reduction of Cholesterol to Key European Targets (SPACE ROCKET) Trial[34] (n=499, 84.0% males, mean age at event 57.7±8.4 years); (iii) MI cases recruited in the Outcomes from Percutaneous coronary intervention by Evaluation of Risk Attributes (OPERA) Trial (n=337, 75.5% males, mean age at event 55.8±8.4 years) and (iv) cases (n= 253, 73.5% males, mean age at event 49.6±7.6 years; 66% MI, 34% PTCA/CABG) from the British Heart Foundation Family Heart Study (BHF-FHS)[35] additional to those used in

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the initial WTCCC Study. Case status in all studies was validated by direct review of clinical notes. All cases were of White European origin. Controls comprised subjects from the United Kingdom 1958 Birth Cohort (n=4246, 56.1% males, 44 yrs mean age)

Stage 3 Studies

Corogene

The aim of this study is to collect 5000 patients assigned for coronary angiogram in Helsinki University Central Hospital. A further aim is to record echocardiograms of the aortic valves in 3500 consecutive patients undergoing coronary angiography. All patients that give informed consent will be included into this prospective study. Peripheral blood leukocyte DNA will be collected, and the patients will be genotyped for a number of candidate genes related to inflammation, immunologic responses, and regulation of lipid and bone metabolisms. The echocardiographic changes of the aortic valve, stiffening, thickening, calcification and flow obstruction will be assessed[36].

FINCAVAS

The Finnish Cardiovascular Study (FINCAVAS) participant pool consists of patients who were recruited during 2001-2007 who underwent exercise stress tests at Tampere University Hospital, follow-up data was gathered at 2, 5 and 10 years. All the consecutive patients coming in for an exercise stress test and willing to participate in the study are recruited between with the aim to recruit roughly 5,000 patients. The study protocol was approved by the Ethical Committee of the Hospital District of Pirkanmaa, Finland, and all patients have given informed consent prior to the interview and measurements as stipulated in the Declaration of Helsinki. Cases are defined as >50% stenosis in one or more coronary arteries in coronary angiography, or strong Bayesian posterior probability for CAD after exercise test using a bicycle ergometer, or hospital verified myocardial infarction in medical history. Controls were defined as <50% stenosis in coronary arteries, or low Bayesian posterior probability for CAD after exercise test, and no myocardial infarction in medical history[37].

GenRIC

The Genomics Research in Cardiovascular disease (GenRIC) is an East Asian study were participants were recruited in Seoul, South Korea. Cases were selected from hospital admissions meeting the following phenotype criteria. Angiographic definition: significant reduction in luminal diameter due to coronary atheromatous disease (i.e. with stenosis greater than 50%). Clinical definitions: Stable angina: chest or arm discomfort that may not be described as pain but is reproducibly associated with physical exertion or stress and is relieved within 5-10 minutes by rest and/or sublingual nitroglycerin (Ref. Harrison's Principles of Internal Medicine; Longo et al), Unstable angina: Angina pectoris or equivalent ischemic discomfort with at least one of three features
1) it occurs at rest, usually resting > 10 minutes, 2) it is severe and of noew onset (≤4-6 weeks), 3) it occurs with a crescendo pattern (Ref. Harrison's Principles of Internal Medicine; Longo et al), Myocardial infarction: Spontaneous or secondary myocardial infarction according to the "universal definition of myocardial infarction"[38]. Controls are participants of a population based study that do not present the CAD phenotype and were matched to cases by sex and age.

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2. Background information on novel coronary artery disease risk loci

IL6R

This gene encodes a subunit of the interleukin 6 (IL6) receptor complex. Interleukin 6 is a potent pleiotropic cytokine that regulates cell growth and differentiation and activation may lead to the regulation of the immune response, acute-phase reactions and hematopoiesis. The IL6 receptor is a protein complex consisting of this protein and interleukin 6 signal transducer (IL6ST/GP130/IL6-beta), a receptor subunit also shared by many other cytokines. A pseudogene of this gene is found on chromosome 9, alternatively spliced transcript variants encoding distinct isoforms have been reported and a short soluble form may also be released from the membrane by proteolysis. Low concentration of the soluble form acts as an agonist of IL6 activity. Dysregulated production of IL6 and this receptor are implicated in the pathogenesis of many diseases, such as multiple myeloma, autoimmune diseases and prostate cancer. Common variants in *IL6R,* effect allele rs4129267-T (r^2 of 0.542 with lead CAD SNP rs4845625 in **Table 2**), have been associated with asthma[39] and decrease in levels of C-reactive protein[40].

ABCG5 - ABCG8

The ABCG5 and ABCG8 genes are tandemly arrayed on chromosome 2, in a head-to-head orientation, the proteins are members of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. The proteins form heterodimers that function as a transporter that appears to play a role in the selective transport of the dietary cholesterol in and out of the enterocytes and in the selective sterol excretion by the liver into bile. It is expressed in a tissue-specific manner in the liver, colon, and intestine.. Mutations in these genes may contribute to sterol accumulation and atheroschlerosis, and have been observed in patients with sitosterolemia. Sitosterolemia patients have hypercholesterolemia, very high levels of plant sterols in the plasma, and frequently develop tendon and tuberous xanthomas, accelerated atherosclerosis and premature coronary artery disease. In a meta-analysis of 16 population-based cohorts, ABCG5 has been associated to serum lipid levels (total cholesterol, $P = 1.5 \times 10^{-11}$; LDL, $P = 2.6 \times 10^{-10}$)[41]. Common variants in ABCG8 and ABO (also a CAD risk locus) have been associated with serum phytosterol levels[42]. Effects in ABCG8 were independently related to SNPs rs4245791 (r^2 of 1 with the lead CAD SNP rs6544713) and rs41360247 r^2 of 0.047 with the lead CAD SNP rs6544713) which showed combined P-values of 1.6×10^{-50} and 6.2×10^{-25}, respectively (n=4412). Serum campesterol was elevated 12% for each rs4245791 T-allele also associated with 40% decreased hepatic ABCG8 mRNA expression[42] (P=0.009).

APOB

Apolipoprotein B (APOB) is the primary apolipoprotein of low-density lipoproteins (LDL) which is responsible for carrying cholesterol to tissues. The protein occurs in the plasma in 2 main isoforms, APOB48 and APOB100. The first is synthesized exclusively by the small intestine, the second by the liver, both isoforms are coded by a single mRNA transcript. APOB48 is generated when a stop codon (UAA) at residue 2153 is created by RNA editing, a tissue-specific splicing gene determines which isoform is ultimately produced. APOB48 lacks APOB100's C-terminal LDL receptor binding region. Apo B-100 functions as a recognition signal for the cellular binding and internalization of LDL particles by the apoB/E complex. High levels of APOB can lead to plaques that cause vascular disease (atherosclerosis), leading to heart disease. APOB100 levels are a better indicator of cardiovascular disease risk than total cholesterol or LDL. Hypobetalipoproteinemia is a genetic disorder that can be caused by a mutation in the APOB gene. Mutations in this gene or its regulatory region cause hypobetalipoproteinemia, normotriglyceridemic hypobetalipoproteinemia, and hypercholesterolemia due to ligand-defective apoB, diseases affecting plasma cholesterol and apoB levels. Mice overexpressing mApoB have increased levels of LDL and decreased levels of HDL Mice containing only one functional copy of the mApoB gene show the opposite effect, being resistant to hypercholesterolemia. Mice containing no functional copies of the gene are not

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viable. APOB has been associated to serum lipid levels: rs1367117-A increases total cholesterol (4.16 [3.73-4.59] mg/dL) and LDL-cholesterol (4.05 [3.68-4.42] mg/dL) whereas rs1042034-C increases HDL-cholesterol (0.9 [0.72-1.08] mg/dL) and decreases triglycerides (5.99 [5.11-6.87] mg/dL)[43]. However, our lead CAD SNP rs515135 has low LD with the above two SNPs (r^2 of 0.135 with rs1367117 and 0.033 with 1042034). As reported in **Supplementary Table 5** rs515135 was strongly asociated for total and LDL chrolesterol in that same study.

ZEB2-AC074093.1

Zinc finger E-box-binding homeobox 2 (*ZEB2)* is a transcriptional inhibitor that binds to DNA sequence 5'-CACCT-3' in different promoters, represses transcription of E-cadherin. Mutations in the ZEB2 gene are associated with the Mowat-Wilson syndrome, a complex developmental disorder characterized by mental retardation, delayed motor development, epilepsy, microcephaly and a wide spectrum of clinically heterogeneous features suggestive of neurocristopathies at the cephalic, cardiac, and vagal levels.
Activin A type II receptor (ACVR2A). Activins are dimeric growth and differentiation factors which belong to the transforming growth factor-beta (TGF-beta) superfamily of structurally related signaling proteins. Activins signal through a heteromeric complex of receptor serine kinases. On ligand binding, forms a receptor complex consisting of two type II and two type I transmembrane serine/threonine kinases. Type II receptors phosphorylate and activate type I receptors which autophosphorylate, then bind and activate SMAD transcriptional regulators. The protein is a receptor for activin A, activin B and inhibin A

VAMP5 - VAMP8 - GGCX

Vesicle-associated membrane protein 8 (VAMP8) is involved in the targeting and/or fusion of transport vesicles to their target membrane. Involved for dense-granule secretion in platelets. Plays a role in regulated enzyme secretion in pancreatic acinar cells. Involved in the abscission of the midbody during cell division, which leads to completely separate daughter cells. Involved in the homotypic fusion of early and late endosomes.

Gamma-glutamyl carboxylase (GGCX) is an enzyme that catalyzes the posttranslational modification of vitamin K-dependent proteins. Many of these vitamin K-dependent proteins are involved in coagulation so the function of the encoded enzyme is essential for hemostasis. Most gla domain-containing proteins depend on this carboxylation reaction for posttranslational modification. Defects in GGCX are a cause of combined deficiency of vitamin K-dependent clotting factors type 1 (VKCFD1). In humans, the gamma-glutamyl carboxylase enzyme is most highly expressed in the liver

GUCY1A3

Guanylate cyclase soluble subunit alpha-3 is an enzyme that in humans is encoded by the *GUCY1A3* gene. Soluble guanylate cyclase (sGC), a heterodimeric protein consisting of an alpha and a beta subunit, catalyzes the conversion of guanosine-5'-triphosphate (GTP) into 3',5'-guanosine monophosphate (cGMP) and pyrophosphate and functions as the main receptor for nitric oxide. Nitric oxide affects IL-6, which is the ligand for IL6R (see above), expression in human peripheral blood mononuclear cells involving cGMP-dependent modulation of NF-κB activity[44]. Key physiological roles for guanylyl cyclases include regulation of cell hyperplasia, hypertrophy, migration, extracellular matrix production, cell differentiation and tumor progression. In addition, guanylyl cyclases mediate important communication between the heart, intestine and kidney to regulate blood volume and Na+ balance.

EDNRA

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Endothelin receptor type A, is a human G protein-coupled receptor that has been shown to interact with HDAC7A and HTATIP. This family of receptors are located primarily in the vascular smooth muscle where they play a role in vasoconstriction and cell proliferation. This gene encodes the receptor for endothelin-1, a peptide that plays a role in potent and long-lasting vasoconstriction, Isoform 1, isoform 3 and isoform 4 are expressed in a variety of tissues, with highest levels in the aorta and cerebellum. This receptor associates with guanine-nucleotide-binding (G) proteins. Polymorphisms in this gene have been linked to migraine headache resistance. Alternative splicing results in multiple transcript variants. In a recent study rs1878406-T has been associated with a .0087 [0.01-0.01] per unit increase in carotid intima media thickness and .1993 [0.14-0.26] per unit increase in plaque[45].

SLC22A4 - SLC22A5

Solute carrier family 22, member 4 (SLC22A4), the encoded protein is an organic cation transporter and plasma integral membrane protein containing eleven putative transmembrane domains as well as a nucleotide-binding site motif, the protein is responsible for the cotransport of sodium ions and ergothioneine, which is an antioxidant, into cells. Widely expressed. Highly expressed in whole blood, bone marrow, trachea and fetal liver, highly expressed in intestinal cell types affected by Crohn disease, including epithelial cells. Genetic variations in SLC22A4 are a cause of susceptibility to Crohn‘s disease[46].

Solute carrier family 22, member 4 (SLC22A5), is a membrane transport protein associated with primary carnitine deficiency. Polyspecific organic cation transporters in the liver, kidney, intestine, and other organs are critical for elimination of many endogenous small organic cations as well as a wide array of drugs and environmental toxins. The encoded protein is involved in the active cellular uptake of carnitine. Mutations in this gene are the cause of systemic primary carnitine deficiency (CDSP), an autosomal recessive disorder manifested early in life by hypoketotic hypoglycemia and acute metabolic decompensation, and later in life by skeletal myopathy or cardiomyopathy. Strongly expressed in kidney, skeletal muscle, heart and placenta.

Both SLC22A4 and SLC22A5 are located in the same recombination interval with IL5 at 5q31.1. The 5q31.1 region has been associated with fibrinogen levels (rs2522056), eosonophil numbers (rs4143832; near *IL5*), C-reactive proteinlevels (rs4705952; near *IRF1*) and Crohn’s disease (rs12521868; near *C5orf56*). We found no evidence of association with CAD risk for rs4143832, rs4705952 and rs12521868; rs2522056 was not tested in our study.

KCNK5

The potassium channel subfamily K member 5 (*KCNK5*) gene encodes $K_{2P}5.1$, one of the members of the superfamily of potassium channel proteins containing two pore-forming P domains. The gene is mainly expressed in the cortical distal tubules and collecting ducts of the kidney. The protein is highly sensitive to external pH and this, in combination with its expression pattern, suggests it may play an important role in renal potassium transport.

PLG

Plasmin is released as a zymogen called plasminogen (PLG) from the liver into the systemic circulation. Plasminogen is converted into active plasmin by a variety of enzymes, including tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA), kallikrein, and factor XII (Hageman factor). Plasmin is a serine protease that acts to dissolve fibrin blood clots. The conversion of plasminogen to plasmin involves the cleavage of the peptide bond between Arg-560 and Val-561, two transcript variants encoding different isoforms have been found for this gene. Deficiency in plasmin may lead to thrombosis, as clots are not degraded adequately. Its role in tissue remodeling and tumor invasion may be modulated by CSPG4.

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HDAC9

Histone acetylation/deacetylation alters chromosome structure and affects transcription factor access to DNA. The Histone deacetylase 9 gene has sequence homology to members of the histone deacetylase family, histone deacetylation gives a tag for epigenetic repression and plays an important role in transcriptional regulation, cell cycle progression and developmental events. Multiple alternatively spliced transcripts have been described for this gene. This encoded protein may play a role in hematopoiesis, inhibition of skeletal myogenesis, involvement in heart development and protection of neurons from apoptosis, both by inhibiting JUN phosphorylation by MAPK10 and by repressing JUN transcription via HDAC1 recruitment to JUN promoter. HDAC9 has been associated to large vessel ischemic stroke[47].

LPL

Lipoprotein lipase (LPL) is a water soluble enzyme that hydrolyzes triglycerides in lipoproteins, such as those found in chylomicrons and very low-density lipoproteins (VLDL), into two free fatty acids and one monoacylglycerol molecule. It is also involved in promoting the cellular uptake of chylomicron remnants, cholesterol-rich lipoproteins, and free fatty acids. LPL requires APOC2 acts as a coactivator of LPL activity in the presence of lipids on the luminal surface of vascular endothelium. LPL is attached to the luminal surface of endothelial cells in capillaries. It is most widely distributed in adipose, heart, and skeletal muscle tissue. Defects in LPL are the cause of lipoprotein lipase deficiency also known as familial chylomicronemia or hyperlipoproteinemia type I. Women with LPL deficiency have been reported to have a significantly higher risk of coronary artery disease ($P = 0.013$)[48]. The S447X variant of *LPL* has been inversely associated with severity of coronary artery disease suggesting a protective role[49].

TRIB1

Tribbles homolog 1 belongs to the protein kinase superfamilyand interacts with MAPK kinases and regulates activation of MAP kinases. Expressed in most human tissues with the highest levels in skeletal muscle, thyroid gland, pancreas, peripheral blood leukocytes, and bone marrow.

FURIN- FES

Furin is in the upstream region of the oncogene FES, the gene was known as FUR (FES Upstream Region) and therefore the protein was named furin. Furin is enriched in the Golgi apparatus, where it functions to cleave other proteins into their mature/active forms downstream of a basic amino acid target sequence (RX(K/R)R consensus motif). This gene is thought to play a role in tumor progression, expression of furin in T-cells is required for maintenance of peripheral immune tolerance. Furin is also utilized by a number of pathogens, the envelope proteins of HIV, influenza and dengue fever viruses must be cleaved by furin or furin-like proteases to become fully functional. Anthrax toxin, pseudomonas exotoxin, and papillomaviruses must be processed by furin during their initial entry into host cells.

The FES gene encodes the human cellular counterpart of a feline sarcoma retrovirus protein with transforming capabilities. The gene product has tyrosine-specific protein kinase activity and that activity is required for maintenance of cellular transformation. Its chromosomal location has linked it to a specific translocation event identified in patients with acute promyelocytic leukemia but it is also involved in normal hematopoiesis as well as growth factor and cytokine receptor signaling. Alternative splicing results in multiple variants encoding different isoforms. Can act as proto-oncogene in some types of cancer, possibly due to abnormal activation of the kinase. but as tumor suppressor in other types of cancer.

FLT1

Oncogene FLT belongs to the src gene family and is related to oncogene ROS, like other members of this family, it shows tyrosine protein kinase activity that is important for the control of cell proliferation and

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differentiation. This gene encodes a member of the vascular endothelial growth factor receptor (VEGFR) family. VEGFR family members are receptor tyrosine kinases (RTKs) which contain an extracellular ligand-binding region with seven immunoglobulin (Ig)-like domains, a transmembrane segment, and a tyrosine kinase (TK) domain within the cytoplasmic domain. Multiple transcript variants encoding different isoforms have been found for this gene, isoforms include a full-length transmembrane receptor isoform and shortened, soluble isoforms. The soluble isoforms are associated with the onset of pre-eclampsia. This protein binds to VEGFR-A, VEGFR-B and placental growth factor and the VEGF-kinase ligand/receptor signaling system plays a key role in vascular development and regulation of vascular permeability. Isoform SFlt1 may have an inhibitory role in angiogenesis. Detected in normal lung, but also in placenta, liver, kidney, heart and brain tissues. Specifically expressed in most of the vascular endothelial cells, and also expressed in peripheral blood monocytes and placental trophoblast cells.

3. Network analysis in genes not associated to CAD

In a control experiment for the network analysis we tested the bottom (least significant) 1,885 SNPs of the FDR analysis. We assigned 369 genes to this SNP set based on physical proximity and subjected them to network analysis with the Ingenuity Pathway Analysis software under the same conditions used for the CAD set (FDR <10%). We note that SNP content on the Metabochip array is not random as it has been selected for association to a number of different traits. In addition, the Metabochip includes the NHGRI GWA catalogue of significantly associated SNPs (July 2009). Therefore, we expect some level of connectivity between genes when assessing the non CAD associated set.
IPA analysis generated ten networks and two overlapping networks (ON). One ON comprised networks1, 5-6) and the other networks 3 and 7. Connectivity in the CAD set was significantly higher (4 networks, one with 6 modules, one with two and two singletons). The genes in the seven networks are enriched for genes known to be involved in cell-to-cell signaling and interaction ($P = 1.32 \times 10^{-4}$), cellular growth and proliferation ($P= 1.71 \times 10^{-4}$) and carbohydrate metabolism ($P = 2.27 \times 10^{-4}$). No significant enrichment was observed for lipid metabolism (P= 2.27E-04) which we found in the CAD associated set ($P= 7.11 \times 10^{-10}$). Looking at enrichment under the Physiological System Development and Function terms the top one was behavior ($P = 8.39 \times 10^{-6}$) as opposed to tissue morphology (size and area of atherosclerotic lesion, quantity of leukocytes, macrophages and smooth muscle cells; $P = 9 \times 10^{-10}$) in the CAD set. No enrichment was found for immune cell trafficking (migration and adhesion) which reached $P = 9.38 \times 10^{-8}$ in the CAD set. Based on disease terms the molecules in the control set are enriched for Immunological disease (1.79 x 10E-13) as opposed to the CAD set which is as expected enriched for Cardiovascular Disease (7.89 x 10E-10).

Finally, when looking at the canonical pathways mapping to the seven networks the most significant were

Name	**p-value**	**Ratio**
Hepatic Cholestasis	2.79E-04 9/146	(0.062)
GNRH Signaling	5.92E-04 8/136	(0.059)
Molecular Mechanisms of Cancer	6.93E-04 14/367	(0.038)
Nicotinate and Nicotinamide Metabolism	8.5E-04 7/101	(0.069)
TGF-b Signaling	1.6E-03 6/89	(0.067)

In addition to an overall weaker representation of query molecules in the top five pathways compared to the CAD set (**Figure 2A** main text) the top two pathways, Hepatic Cholestasis and GNRH Signaling, which include 146 and 136 members respectively, do not contain any gene in the 47 CAD genome-wide significant loci (Table **1** and **2** main text).

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